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# PATHOLOGY

A MANUAL FOR TEACHERS AND  
STUDENTS

BY

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**THIS WORK IS AFFECTIONATELY DEDICATED TO THE MANY  
STUDENTS OF PATHOLOGY FROM ASSOCIATION  
WITH WHOM I HAVE DERIVED THE  
GREATER PROFIT**



## PREFACE

THIS manual has developed from the Syllabus of Pathology published by Councilman and Mallory in 1904, and is designed with special reference to the teaching of the subject. The work gives the plan which has been followed in teaching pathology in the Harvard Medical School, and which has proven to be successful. The central feature is that opportunity shall be given the student to acquire knowledge of the subject by the exercise of his own powers. To this end laboratory work embracing the study of the gross and the microscopic changes in the tissues and organs and the alterations in function produced by disease, is made the main feature. This work is supplemented by lectures which have the object not of conveying new information, but of expanding and co-ordinating the knowledge which the student himself has acquired.

Illustrations were purposely omitted in the work. Excellent and accurate as are most of the illustrations in the current textbooks of Pathology, they still, when objective, represent areas carefully selected for the illustration of a point, more commonly being the author's interpretations. It is much better that the student should make his own illustrations from the objects studied. Drawing is a mode of expression too often neglected. It helps enormously in accuracy of observation, and by a drawing the student often can convey his conception of an object more clearly than by writing. Blank leaves are inserted after the various chapters, on which the student should make notes of conditions observed, and illustrate these with original drawings. In this way he will contribute to the creation of a book which will be of value to him, the most valuable portion being his own contribution.

In the text there is considerable difference in the fullness with which the various subjects have been treated. This is particularly true in regard to the treatment of the infectious diseases and the special pathology of organs. The thorough treatment of certain subjects and the small allowance given to others is not meant as an index of their relative importance, but the fuller description is given to those conditions which illustrate principles of wide appli-



cation. The work does not aim at completeness; at present no treatise on pathology to be used as a textbook can have such an object. The absence of any save indirect consideration of the pathology of the central nervous system and of the skin is conspicuous. At various places, both in the general text and in the autopsies, there are numerous references to the pathology of these organs, and their pathology is usually fully considered in the special teaching. The same is true of other organs of which there is scant mention. The student must supplement the text by reading, which includes to as large an extent as possible the original work both of the past and present, on which the conceptions of processes as given are based. The limitation of space has prevented the discussion of controversial points. The views given are the personal views of the author and in most cases are those which are prevalent. Opportunity is given the student to test the conceptions of processes given and to amend them should they seem not to agree with his observations.

The protocols of autopsies added to the various chapters will be found a valuable addition in impressing on the mind the fact that in disease it is the organism and not merely the organ which is affected. Particularly in the study of special pathology the student is likely to think of a diseased liver or kidney as an isolated product rather than of the individual in whom there is a diseased organ. The inter-relation of disease in the individual can be studied in no other way than by the complete autopsy. There is sufficient space for the addition of the protocols of autopsies, which the student sees and assists in, with the histological descriptions of lesions. The illustrative autopsies have been taken from those filed in the Department of Pathology, and represent the work of many men who have been associated with the department and who have in this way materially assisted in the work. These protocols have been used with but little change and correction and represent considerable variation in the thoroughness with which the work was done and in accuracy and completeness of description.

The description of the experiments to be undertaken in connection with the work was written by Assistant Professor Karsner, to whom I am indebted also for reading and revising the manuscript. No course in pathology can be considered at all adequate which does not include experimental work of the character

suggested here. These are to be carried out by groups of students working under direct supervision and the description of the experiments and the inferences to be drawn from them written in the blank pages.

The value of experimental work on the part of the students is great, not only because of the training in the experimental method, but particularly because of the correlation between cause and effect and the living demonstration of altered function. The proper point of view is attained only by the actual participation of the student in the work, for here is the true field for the extension of laboratory study. It must continually be borne in mind, however, that the highest ideal of humanity must be striven for, not in the mere observance of specified rules in regard to anæsthesia and painless termination of experiments, but also in following the spirit of these rules and the practice of kindness and gentleness.



## TABLE OF CONTENTS

	PAGE
INTRODUCTION WITH CONSIDERATION OF TISSUES .....	17-25
ATROPHY .....	26-28
DEGENERATIONS: Cloudy Swelling; Fatty Metamorphosis; Glycogenic degeneration; Muroid degeneration; Amyloid degeneration; Hydropic degeneration; Hyalin degeneration; Colloid degeneration; Calcification; Calculi; Concretions; Incrustations; Pigmentation; Death and Necrosis; Experiments .....	29-45
INFLAMMATION: Vascular phenomena; Exudation and the Exudate; Healing and Repair; Phagocytosis; Granulation tissue formation and cicatrization; Experiments .....	46-59
THE BLOOD: Anæmia; Hæmolysis; Plethora; Hydræmia; Coagulation; Thrombosis; Embolism; Experiments .....	60-70
PATHOLOGICAL ANATOMY OF HEART AND BLOOD VESSELS: Pericardium; Myocardium; Heart Hypertrophy; Endocardium; Veins; Varicose veins; Arteries; Arteriosclerosis; Syphilitic arteriosclerosis; Endarteritis obliterans; Aneurysm .....	71-83
PATHOLOGICAL PHYSIOLOGY OF THE CIRCULATION: Pericardial pressure; Valvular Stenosis and Insufficiency; Cardiac Hypertrophy and Dilatation; Myocarditis; Passive congestion of lungs, liver, spleen, kidneys, intestinal canal, brain; Arteriosclerosis; Hæmorrhage; Œdema; Experiments; Autopsies .....	84-123
GROWTH, HYPERTROPHY, HYPERPLASIA, REGENERATION, METAPLASIA ....	124-130
TUMORS: General Pathology: Metastases; Origins; Cell Characteristics; Inheritance; Œtiology; Classification; Cysts .....	131-148
Special Pathology: Fibroma; Papilloma; Intracanalicular Tumors; Myxoma; Lipoma; Chondroma; Osteoma; Leiomyoma; Hæmangioma; Lymphangioma; Endothelioma; Sarcoma; Neuroma; Glioma; Rhabdomyoma; Lymphoma; Myeloma; Chloroma; Leukemia-Lymphatic; Leukæmia Myelogenous; Adenoma; Adenocystoma; Carcinoma; Chorio-epithelioma; Hypernephroma; Epidermoid Cysts; Cholestatoma; Dermoid Cysts; Experiments; Autopsies .....	149-193
INFECTIOUS DISEASES: Infectious Organisms — Bacteria; Infection from Surfaces; Wound Infection; Phagocytosis; Opsonins; Bacteriolysis; Natural Immunity; Susceptibility; Individual, etc.: Interaction between Tissues and Infectious Organisms; Atrium of Infection; Periods	

	PAGE
of Disease; Antitoxic Action; Germinal Infection; Secondary Infection; Experiments.....	194-209
Special Infections — Staphylococcus Pyogenes Aureus; Streptococcus Pyogenes; Diplococcus pneumoniæ; Diplococcus Intracellularis Meningitidis; Gonococcus; Bacillus Tuberculosis; Leprosy Bacillus; Treponema Pallidum; Streptothrix Actinomyces; Bacillus Mallei; Bacillus Anthracis; Bacillus Diphtheriæ; Bacillus Influenza; Bacillus Tetani; Bacillus Pestis; Bacillus of Soft Chancre; Bacillus Typhosus; Bacillus Dysenteriæ; Spirillum Cholerae Asiaticæ; Bacillus Coli Communis; Entamoeba Histolytica; Plasmodium Malariae; Small Pox; Acute Anterior Poliomyelitis.....	210-330
PARASITIC WORMS: Cestodes (Cysticerci); Nematodes; Distomata; Experiments.....	331-335
SPECIAL PATHOLOGY OF ORGANS: General Considerations applying to Systemic Disease.....	336
PATHOLOGY OF THE KIDNEY.....	337-364
PATHOLOGY OF THE ALIMENTARY CANAL.....	365-371
PATHOLOGY OF THE PANCREAS.....	372-377
PATHOLOGY OF THE LIVER.....	378-389
PATHOLOGY OF THE LUNGS... ..	390-393

## INTRODUCTION

**PATHOLOGY** is the study of disease. Disease may be defined as a change produced in organisms in consequence of which they are no longer in harmony with their environment. The matter which composes the living organism is complex. It is able to receive potential energy and to transform it into those forms of manifest energy, which, considered together, are called the phenomena of life. The elementary substances which enter into living matter are known, and further, it is known that these elements are combined to form a large number of chemical substances most of which are characterized by high molecular weights, but of which the intermolecular arrangement, the chemical structure, is unknown. Nor is much known concerning the structure of living material or protoplasm. The most generally accepted theory of structure is that of network or foam structure with interstices filled with material which differs in its physical character from that of the network. The living matter is heterogeneous and not homogeneous, and in the heterogeneous mass independent chemical processes can take place, the various spheres of action being probably separated from one another by colloid walls. Such a foam structure is not identical with the intracellular reticulum which can be demonstrated by certain histological methods and which is probably an artefact. To such a conception of structure the objection has been raised, that solid substances pass readily from one part of a cell to another; but this could take place with the presence of a reticulum of colloidal character. By microscopical and micro-chemical observation it is possible to detect various substances within cells the chemical nature of some of which is known. Under pathological conditions new substances may be found or those normally present may be increased or diminished or variously altered.

Living matter differs from dead not only in complexity of structure, but in variability of structure to which a variability in reaction is due which constitutes the individuality of the organism. Such individuality is not found in non-living substances, in which, under uniform conditions, the reactions are identical. It results

naturally from this, that disease is always individual. Neither the lesions nor the phenomena are precisely the same in each instance, and the knowledge on which measures for relief are based must come from the investigation of the individual case.

Living matter is adaptable. An organism can so adapt itself to changing conditions that the phenomena exhibited are the usual. Within the species there is variation in the capacity for adaptation as exhibited by different individuals, and there is little doubt that such variations can be inherited. When the conditions acting upon an organism are beyond the range of adaptation, a change is produced in it and its reactions are unusual. The organism is then diseased and the condition which brought about the change is a cause of disease. Any condition acting upon an organism to the action of which the organism cannot adapt itself, that is, cannot in this new environment exhibit the usual phenomena, is a cause of disease.

To pathology there belongs first the study of the changes in the organism to which the abnormal reactions are due. These changes are called lesions. They vary greatly in character and extent, may be so marked as to be easily apparent to sight and touch, or only apparent on microscopical or chemical examination. It is possible for changes to be produced in cells which can be recognized by abnormal reactions only, there being no alteration apparent by either microscopical or chemical investigation. The red corpuscles of an animal which are immunized against the hæmolytic action of a foreign serum show no change and yet they are so altered as to resist the disintegration which takes place in the corpuscles of the non-immune animal under the same condition.

The study must further embrace the cause and the mode of development and the association of lesions. In so complex an organism as man with complete co-ordination of the activities of each part, the inter-relation of lesions is most important. Pathology forces upon us the realization that the body is an organism, not a collection of independent entities, and that while a disease may seemingly be localized in a part, yet through the changed condition of that part the entire organism is diseased.

The study of the lesions alone, even though the steps in their evolution could be traced by a long series of cases, would not lead to a complete comprehension of disease. The present conception of

disease is due mainly to the knowledge of the causes of disease which has come in the last forty years. This knowledge has been obtained chiefly by the use of the experimental method in investigation to a greater extent than ever before, a method which has revolutionized the older conception of the cause, development and processes of disease; has correlated these processes and phenomena with their underlying lesions and has made more rational the classification and nomenclature of disease. The same cause acting in the same body under different conditions may produce lesions which anatomically may differ widely. The best example of this is given by tuberculosis. The discovery of the bacillus tuberculosis and the experimental study of the disease have made it possible to group together such conditions as Pott's disease, caseous pneumonia, scrofula and miliary tuberculosis.

Pathology is to be looked upon as one of the divisions of biological science, and, as such, demands close and patient observation. The student must approach the subject of disease from all possible points of view, utilizing gross anatomical, histo-pathological, and the various experimental methods of study. To ensure accuracy of study careful record of all work should be made both by objective description and careful drawing, the latter being of especial advantage in formulating clear conceptions. By mentally combining the information acquired in these various ways there can be built up a knowledge of disease that will serve as a safe guide for the institution of means to prevent disease and of therapeutic measures to relieve the diseased individual.

The study of pathology presupposes a knowledge of normal structure and function. In the study of normal structure the emphasis is properly laid on the architecture of organs, the inter-relations of the cells and tissues composing them and the mode of construction. While the importance of this is true in the study of pathology, yet of more fundamental importance is the study of the material which enters into the architectural structure. There are certain general conceptions of tissue which it is important to hold in mind in the study of all lesions.

The body is composed of an external surface covered by epithelium which surface is enormously increased by glands which belong to it and an internal surface, also covered by epithelium and with a still greater duplication of surface to form glands.



These surfaces are connected at the mouth and the anus. The internal surface constitutes the alimentary canal and the respiratory system. There is also a third epithelial surface, the genito-urinary system which is connected with the external surface by a single opening. These surfaces all enclose a cavity which is filled with a fluid which comes into close relation with all living parts. It is only by means of such a physical environment that nutrition and the necessary interchange between the living matter and its environment can take place. This cavity is closely packed with cells and with the intercellular substances and contains large spaces or fissures, of which the peritoneal space is an example.

**CELLS AND INTERCELLULAR SUBSTANCES.** It is customary to think of the cells of the body as alone possessing the structure and qualities by which living matter is recognized. The intercellular substances possess some, but not all of these qualities.

**BLOOD AND LYMPHATIC VESSELS.** Aside from the highly differentiated organs, there are certain cells and structures which are found everywhere and which must be considered. The blood vessels are best thought of as a continuous tube lined with flat endothelial cells to which in different parts other elements are added. The simple endothelial tube is represented by the capillaries. These, unless artificially injected or filled with blood corpuscles, are not easily visible. The differentiation of the endothelial tube into the artery takes place by the formation outside of the endothelium of nonstriated muscle cells, these appearing first as single separated fibres, which, by increase in number, form a continuous band. Elastic tissue is formed, represented in the smaller arteries by a band, — the internal elastic lamina, — immediately outside of the endothelium, in the larger by elastic fibres either singly or in bands among and between the muscle fibres. The relative amounts of muscle and elastic tissue differ both according to size and function of the arteries. The larger arteries and those which serve mainly the purpose of conduction have relatively a much greater amount of elastic tissue than the smaller and distributing arteries. The larger arteries have a rather indefinite coat of connective tissue outside of the media, the adventitia, which bears the vasa-vasorum and connects the thick media with the surrounding tissue. On the inside of the media a varying amount of connective tissue is found, which, with the endo-

thelial lining, is known as the intima. From the capillaries the differentiation into veins consists in the formation of a definite connective tissue coat outside of the endothelium, and in the larger veins a considerable amount of muscular tissue, not in the form of a definite coat as in the arteries, but as bands of muscle fibres enclosed in the connective tissue. With this there is a small amount of elastic tissue. In the lung there is so little difference in structure between the arteries and the veins that they are best differentiated by their position in reference to the bronchi. The lymphatic vessels form a system of simple endothelial tubes except in the case of the larger lymph trunks in which the wall contains also connective tissue and muscle fibres. The endothelial cells of the lymphatic vessels are larger and their borders more irregular than the similar cells of the capillaries. It cannot be regarded as absolutely proven whether or not there are actual spaces between the endothelial cells. Such spaces allowing an actual communication between the tissue fluids and the contents of the lymphatics seem to exist. The number of lymphatics is greatly underestimated; they cannot be recognized in sections of tissues unless artificially injected or filled with a fluid which has been coagulated by the hardening.

**CONNECTIVE TISSUE** consists of cells and intercellular substances in fibrillar form. The cells vary greatly in morphology in different parts and under different conditions. The cytoplasm usually is branched peripherally, the nucleus stains lightly, and is usually oval or elongated in shape. In the cornea, by suitable stains, a beautiful system of flat, greatly branching cells can be demonstrated, but such cells cannot be taken as the type of cells of the system in other places. Often the cells in sections are represented merely by a rod-shaped nucleus in close association with bands of fibres. The intercellular substances appear in the form of fibrils which show certain differences in form and in their chemical reactions.

**WHITE FIBROUS TISSUE.** Connective tissue fibrils. These are delicate fibrils wavy in outline, usually to a greater or less extent joined closely together in bundles, this arrangement being best marked in the tendon, or, as in the cornea, they may be arranged in parallel rows forming plates, or, as in the subcutaneous tissue, in the form of a loose mesh work. In many organs the connective

tissue takes the form of a delicate reticulum of closely interwoven fibrils which form an internal skeleton of the organ. Where connective tissue comes in contact with epithelium the fibres are often closely united to form a definite band, the *membrana propria*. Among these fibres there are larger, denser fibres described as fibroglia fibres which have a close relation to the cells and which are most numerous in rapidly growing connective tissue.

ELASTIC TISSUE occurs in the form of a network of fibres or as thin fenestrated plates. The fibres are very refractive in the fresh state, vary greatly in size, are very resistant and are easily demonstrated by certain methods of staining.

There are also fibrils associated with epithelial tissues. These are the epithelial fibrils of the skin, wavy and corkscrew fibrils demonstrated by special stains which pass between and through the epithelial cells, the neurofibrils and neuroglia of the central nervous system and the intracellular fibrils of certain epithelial organs. The neuroglia of the central nervous system is very analogous to the connective tissue both in normal and pathological conditions and like it consists of fibres and cells in more or less definite relation with each other. The fibrils are rarely joined together to form bands. The neuro-fibrils, demonstrated only by special methods of staining, are different from the neuroglia and are more directly associated with the ganglion cells.

THE BLOOD AND THE BLOOD FORMING TISSUES. The red cells in the blood contain hæmoglobin which, when it has been fixed by hardening agents, stains deeply with such acid dyes as eosin. The hæmoglobin is easily dissolved out of the corpuscles in tissues which have not been properly hardened and the corpuscles are then either invisible or appear as pale rings. Red blood corpuscles can be found in practically every section of tissue; the size varies but little in different methods of hardening and they form a good basis for comparative measurement. As seen in sections of tissues hardened in Zenker's fluid, they appear somewhat smaller than in the fresh blood and have an average diameter of  $6\mu$ .

Among the white corpuscles of the blood can be distinguished the polynuclear leucocytes which form 70 to 72 per cent of all the leucocytes. These are larger than the red corpuscles, and the contour is sharp, giving the appearance of a definite membrane. The cytoplasm contains fine round granules which are often lost in

the process of hardening and which take a double stain with acid and basic dyes. The nucleus consists of several masses connected together by fine filaments, the whole having a semicircular or crescentic form. It stains intensely with basic dyes.

**LYMPHOCYTES.** These form 22 to 25 per cent of the white corpuscles. In coverslip preparations of blood a larger and smaller size can be recognized, the smaller greatly predominating. As seen in sections, particularly after hardening in Zenker's solution, the differentiation into smaller and larger cells is not apparent. They are very characteristic cells about the size of the red corpuscles; the nucleus is round and stains brightly, the chromatin having chiefly a peripheral arrangement, the masses at the periphery connected with the intranuclear granules by a chromatin network. Only a small and irregular amount of cytoplasm is visible. This was formerly supposed to be non-granular, but more recently granules of a definite character have been demonstrated.

**EOSINOPHILES.** These form 2 to 4 per cent of the leucocytes. The size of the cell and the characteristics of the nucleus is the same as that of the polynuclear cell, the outline is definite, the cytoplasm contains round granules, easily preserved, larger than the neutrophile granules and which stain intensely with eosin.

**MAST CELLS** form about 0.5 per cent of the leucocytes. The nucleus varies much in character and generally is polymorphous. The cytoplasm contains numerous fairly coarse granules which stain intensely with basic dyes..

**LARGE MONONUCLEAR LEUCOCYTES** form 1 to 3 per cent of the leucocytes. They are the largest of the leucocytes, the nucleus lightly stained, oval, usually horseshoe in shape; the cytoplasm is non-granular, takes no definite stain, and the cell outline is distinct.

**BLOOD PLATELETS** are round or irregular small masses of cytoplasm, 2 to  $3\mu$  in diameter, without nuclei and with large indefinite granules. They easily disintegrate and are not frequently found in sections of tissue in a recognized form but appear as large masses of indefinite granular appearance within blood vessels.

The intercellular substance of the blood, the blood plasma, is a fluid of complex composition. It contains 7.26 per cent of protein which is composed of serum albumen 4.01 per cent; of paraglobulin 2.83 per cent; fibrinogen 0.42 per cent. It contains further numerous extractives, salts and enzymes.

Under normal conditions the red corpuscles, polynuclear leucocytes, the lymphocytes and mast cells are formed in post foetal life in the bone marrow exclusively. They arise by a process of differentiation from cells of an embryonic type in the marrow, only the completely differentiated cells which have no further power of multiplication entering the blood. Under pathological conditions blood formation can take place in other organs, notably in the spleen.

The lymphoid cells of the blood are produced in the lymphoid tissue. This tissue is found chiefly in the form of lymph nodes which are aggregates of lymphoid cells enclosed in a capsule. The cells are enclosed in a reticulum and are arranged into masses and strands by means of a network of channels which connect with the lymphatic vessels entering and leaving the nodes. Cell production takes place in the germinal centres of the nodes which are composed of large cells with an oval vesicular nucleus and a visible cytoplasm. In the germinal centres nuclear figures commonly are found. The channels or sinuses are in close relation to the cells in the follicles and contain a wide-meshed reticulum which, with the walls of the sinuses, is covered with endothelial cells. In addition to the definite nodes small masses of lymphoid tissue not enclosed in definite capsules are found in numerous places. In the intestinal canal between the epithelium and the muscularis mucosa there is a form of lymphoid tissue which differs in some respects from that in the lymph nodes. Cells formed in the nodes pass into the sinuses and thence by means of the efferent lymph vessels into the general lymph stream and the blood.

There is much doubt about the origin of the large mononuclear cells of the blood. They are distinguished from the other blood cells not only by form and structure, but also by function, in that they alone of the leucocytes are phagocytic for other cells, particularly for the lymphocytes. Cells of similar character may be found as free cells in the tissue and in the sinuses of the lymph nodes where they undoubtedly are formed from the lining endothelial cells.

**NERVES.** With the other structures which have been described will be found nerves. Those in the form of medulated fibres in bundles can easily be recognized by the sections of the sheath of Schwann forming in cross or oblique sections circles or ovals enclosing the axis cylinders. Non-medulated fibres even in the form

of bundles of sympathetic fibres are not easily recognized without special modes of staining.

The highly differentiated tissues such as muscle, bone, etc., need not be considered here.

**TISSUE FLUIDS.** All the structures which have been mentioned are impregnated with or surrounded by the tissue fluid. The contents of the blood and lymphatics are separated from the tissue fluids by thin protoplasmic membranes, possibly containing minute spaces at the line of juncture of the cells composing them. Such walls are osmotic, filtering membranes, and the thin, probably colloidal, walls allow cells and, to some extent, probably other solid substances to pass through without rupture. The flow of the blood is towards the tissues, that of the lymphatics away from the tissues. The tissue fluid receives constant addition from the blood, and it is constantly depleted by the lymph outflow. Both interchanges take place through membranes and neither the blood fluid nor the lymph can be taken as representing the tissue fluid. Soluble substances can diffuse through it and it is not impossible that there are movements and currents in it. It also contains cells which are the free cells of the tissue and in pathological conditions these cells can be increased in number and other cells added to them, such as polynuclear leucocytes, large mononuclear cells or endothelial cells and lymphoid cells. By means of the tissue fluid all cell interchange takes place, by it all substances, whether simply nutritive or toxic, are brought to the cells and all products of secretion and metabolism removed.



25b



25 c



25e



**25 g**



## ATROPHY

By atrophy is understood a decrease in size, with or without a numerical decrease, in the cells or essential tissue of an organ. The condition usually is followed by a diminution in the gross size and weight. Exception to this may be found as in emphysema of the lungs, where there is a great reduction in the amount of lung tissue, but owing to the accompanying dilatation of the air spaces the lung may be increased in size. In certain forms of muscle atrophy there may be extensive formation of fat between the atrophied muscle fibres and both size and weight of the muscles increased. The condition of atrophy is to be distinguished from that of hypoplasia, in which there is defective development or growth. Atrophic organs are rather firmer and tougher than normal, for the connective tissue does not undergo atrophy to the same degree as the parenchymatous cells, and may even increase in amount. There usually is also an increased depth of color as in brown atrophy of the heart. The tissue changes in atrophy vary greatly. In atrophy of fat the fat globules within the cells are broken up and the cells either disappear or return to an undifferentiated condition, or the tissue fluid may be increased, forming a gelatinous oedema. In atrophying muscles there may be a large increase in the number of the sarcolemma nuclei. Atrophy may be associated with various degenerations particularly fatty degeneration. A distinction between active and passive atrophy is to be made, the former a primary change in the cells which diminishes their nutrition, the latter an atrophy due to deficient food supply. According to the cause the following forms of atrophy may be distinguished.

**PHYSIOLOGICAL ATROPHY.** The atrophy which certain organs undergo at age periods, as the atrophy of the thymus, the atrophy of the ovaries at the menopause, etc.

**ATROPHY FROM MALNUTRITION.** This includes both atrophy from deficiency of food, and atrophy in consequence of defective blood supply. In starvation all the tissues atrophy in varying degree, the loss being most marked in the fat and muscular tissue.

**PRESSURE ATROPHY.** In this there probably is the combined action of the effect of pressure exerted on the blood vessels interfering with nutrition and direct effect of pressure on the cells. The best example of atrophy from pressure is given in the deep furrow across the liver produced by constriction of the waist. The atrophy of the kidney in hydronephrosis is due in part at least to the interference with the circulation in consequence of the increased pelvic and intratubular pressure.

**ATROPHY FROM DISUSE.** There is a close relation between the nutrition and function of tissues, and disuse results in atrophy. There is a slower circulation in inactive organs and the functional intracellular changes seem to be essential for the nutritive activity. The atrophy of an immobilized fractured extremity is an example.

**NEUROPATHIC ATROPHY.** Atrophy may be seen in parts in which the normal nerve supply has been interrupted or impaired. The causal relation here is complicated, for there usually is interference with the circulation in consequence of the loss of vaso-motor activity, impairment of function and the action of trauma due to loss of sensation. Whether or not the nerves affect the nutrition of cells independently of the conditions which necessarily accompany loss of nerve supply has never been satisfactorily determined.

**SENILE ATROPHY.** Atrophy is the most important of the phenomena of age. It is seen in the loss of hair and teeth, in the thinning of the corium, in the weakening of the supporting tissues giving greater effect to gravity, in the evidence of diminution in function of all organs and in loss of weight, of individual organs. The loss of weight of the entire body is not so apparent owing to the frequent tendency to fat formation. The reserve force is diminished; life is carried on with the full use of all the force of the body, and is so ordered as to make the least demands on function. Senile atrophy is complex in its causes and modes of production. The atrophy affects different organs in different degree and shows in individuals great variation in situation, in degree and in progress. All the causes of atrophy are associated in senile atrophy. Malnutrition due to diseases of the blood vessels plays an important part. To this must be added the effect of organic disease with the necessary impairment of function. In the regular course of life, slight injuries of organs are constantly being produced, which are in part repaired and in part remain, and are compensated for by



greater activity in other parts. In advancing age there is experienced the effect of the sum of injuries, together with a diminished power of repair, and diminution in the reserve power of function. In addition certain tissues of the body, such as arterial walls, seem to wear out in the course of time, perfectly normal arteries being rare after the age of forty. So constant are these vascular lesions that they seem almost sufficient in themselves to explain the senile atrophy. Even the diminution in power of regeneration and repair is certainly in part due to the difficulty of provision of increased vascularity arising from disease of the vessels. But apart from the action of these conditions, there is probably in other organs something of the same change which is seen in arteries but is less manifest. Animals which are but little or not at all the subject of senile arterial change show senile changes much the same as those which occur in man.

## DEGENERATIONS

Certain changes which the cells and tissues of the body undergo in consequence of the action of injurious conditions are classed together as degenerations. Degeneration may affect both the cells and the intercellular substances; in certain cases it is most marked in a single organ, in others more generally distributed.

**CLOUDY SWELLING** is the most common of the degenerations. It is produced by the action of toxins as in the acute infectious diseases, results from insufficient blood supply as in high-grade anæmia, and may be produced experimentally by subjecting the tissues to the action of a variety of injurious agents as, for example, cantharadin. Macroscopically, the affected organs are slightly increased in size, paler and more opaque than normal. The appearance has been aptly compared to that presented by tissues which have been boiled. When examined fresh, the cells are more granular than normal, the granulation often obscuring the nucleus. The granules disappear on the addition of acetic acid or caustic potash. The condition is best studied in the epithelial cells of the kidney and liver and in the muscle cells of the heart. Sections of the kidney show the cells, particularly those of the convoluted tubules, swollen, the edges often broken and irregular, the striated border partly or wholly absent, the cell granules irregular in size and arrangement, and usually vacuolation of the protoplasm. There is no evidence of an increase in the amount of cell material. The change seems to consist in an increase in the amount of intracellular fluid with the precipitation in granular form of substances previously in solution. It is indicative of a minor degree of injury from which the cell can recover.

**FATTY METAMORPHOSIS.** Fat in the form of neutral fat is contained in most of the tissues of the body. In certain organs, as in the kidney of man, it can be demonstrated only by chemical methods. This is so either because it is in some way combined with the protein of the cell or is present in granules so fine as to be invisible microscopically. Fat is found chiefly in the fat depots of the body and in the liver. Almost invariably some fat is found

in the liver and the amount here can be greatly increased so that the excess represents a pathological condition. In consequence of a diet rich in fats or carbohydrates, abnormally large quantities of fat may be brought to the liver and stored there, or in consequence of conditions which interfere with oxidation processes the stored fat is not consumed. The liver cells can contain fat in such large amounts as to resemble fat cells. Such fat is found chiefly in the periphery of the lobules, and may exist without any evidence of other alteration in the cell than diminution of the cytoplasm. In certain organs, as in the heart, the increase of the normal fat tissue may constitute an injury. The normal fat of the pericardium can be very greatly increased and even, particularly in the right ventricle, grow into the myocardium separating the fibres. The mass of inert tissue here increases the work of the heart and the fat substituted for myocardium does not so well resist intracardiac pressure. In organs which have undergone atrophy large amounts of fat may be formed, replacing the atrophied tissue as in muscles long in disuse. All these forms of fat formation are called fatty infiltration. By fatty degeneration is meant the appearance of fat in association with cell degeneration. Such fatty degeneration may produce but little alteration in the appearance of the tissue to the naked eye, particularly when it is diffusely distributed. The alterations are much more evident when the degeneration is focal. The fat in fatty degeneration may be merely the normal fat previously combined with protein, and, owing to change in the cell, separated from this combination; or it may be fat which is brought to the cell from without and which the cell, owing to degeneration, cannot metabolize. The old view that the fat is formed directly from the protein of the cell is no longer held. In fatty degeneration the fat usually is in the form of small granules which can be distinguished in fresh tissues by their refraction and by their persistence after the addition of strong acetic acid. After most methods of hardening, the fat is dissolved by the alcohol. The best method of demonstration is by staining with Scharlach R frozen section of organs which have been hardened in formalin. The fat in the cells varies in amount from a few granules to a seeming substitution of all of the cytoplasm by fat. Connective tissue cells may appear, when stained, as branched granular masses. The cells show other changes in addition to the fat, and often the fat seems merely an

addition to, or further progress of, cloudy swelling. In tissues in which there is extensive fatty degeneration, the fat may be present in the intercellular substances also, appearing in the form of a very fine emulsion. In such cases it is not certain whether the emulsion is in the tissue fluid and results from the destruction of fatty degenerated cells, or whether there is an actual formation of fat in the fibrils. The amount of fat often seems too great to be of cell origin. The presence of fat in the endothelial cells of vessels is an important means of recognizing early degeneration. In degeneration of nervous tissues fat is formed from the myelin. Where tissue containing fat undergoes solution in the body setting the fat free, large phagocytic cells which take up the fat are constant. These are known as compound granule cells, or, from their discoverer, as Glüges corpuscles. Fatty degeneration is a common lesion in the body; it may be produced by the action of many poisons, by conditions of anæmia both local and general and by most of the bacterial infections. Fat crystals occasionally are found free in the cells or tissues. Needle-shaped crystals of fatty acids may be found within necrotic fat cells, in decomposed pus, in gangrenous tissue and in tissue in which there is extensive fatty degeneration. *Cholestrin* is found under somewhat the same conditions, but has not the same relation to decomposition. It appears in tissues as characteristic, flat rhomboidal plates, where there is slow destruction of cells and where the circulation is imperfect, and in fluids where pathological secretions or exudations are long retained. It also forms one of the most important constituents of biliary calculi. In fluids its presence can be recognized by the naked eye by the refractive glistening scales. As tissues ordinarily are hardened cholestrin is dissolved by the alcohol leaving narrow fissures in the walls of which foreign body giant cells may be present.

**GLYCOGENIC DEGENERATION.** Glycogen normally is found in certain tissues of the body, particularly in the liver, muscle and cartilage. It is readily soluble in water and for its detection, tissues should be hardened in absolute alcohol and stained with iodine which colors the glycogen brown. It is found in abundance in some of the tumors, in the leucocytes in certain inflammatory exudations and in the cells of most organs in diabetes. It occurs in the cells only and in the form of granules, globules, or irregular masses. Rarely, it may be found in the nuclei. In diabetes glycogen is

found in large amounts in the cells of Henle's loops constituting a characteristic lesion.

**MUCOID DEGENERATION.** Mucin normally is found as a secretion of the epithelial cells, particularly the cylindrical cells of the intestinal villi and in the interstices of connective tissue, especially of tendon. It is a glassy, viscid substance, dissolves readily in weak alkaline solutions and is precipitated by acetic acid. It is more abundant in foetal than in adult tissue, the umbilical cord being the type of connective tissue containing a large amount of mucin. In hardened tissues it may be recognized by its staining with basic dyes. It has its chief importance in connection with tumors, where it often is found in large amounts. In addition to its presence in tumors it is formed in increased amounts in degenerative conditions of the connective tissue especially in association with defective nutrition. It may be formed in greatly increased amounts in the intestinal epithelium. There are a number of substances termed pseudomucins which have the physical characteristics of mucin but differ from it in reaction.

**AMYLOID DEGENERATION.** Amyloid is a homogeneous, firm substance, never found in normal tissues and occurs pathologically not in cells but as an infiltration of the intercellular tissue. Chemically, it is a protein compound of chondroitin-sulphuric acid and gives a characteristic stain both with iodine and with methyl violet. With iodine it stains mahogany brown and with the methyl violet a rose pink. It occurs in conditions of chronic disease such as tuberculosis, long standing suppurations especially those connected with bone and very commonly is found in old cases of syphilis. The organs which are the seat of amyloid deposits, usually are enlarged, of firm consistency and pale with a peculiar waxy refraction. It occurs by predelection in certain organs, the order being spleen, liver, kidneys, adrenal glands, mucous membrane of intestine and the lymph nodes. Of all the tissues of the body the small arteries are most frequently affected. Here it occurs in the muscular coat at first as masses surrounding and finally supplanting the muscle fibres. It has never been found in the blood nor is it deposited on the inner wall of blood vessels. The general conclusion is that it is formed in the tissues these supplying the protein which unites with chondroitin-sulphuric acid contained in the blood. Occasionally rather ill-defined crystallization is seen in amyloid and this is more

common in the amyloid of lower animals, particularly the mouse. The presence of amyloid in tissue is associated always with atrophy and other forms of degeneration, due principally to the interference with nutrition occasioned by the amyloid masses around the vessels. It is uncertain whether or not amyloid ever disappears from the tissue.

In the spleen amyloid may appear only in the media of the arteries or as an infiltration around the fibres of the reticulum of the follicles or as a more diffuse infiltration of the pulp.

In the liver amyloid appears first around the arteries, then around the capillaries in the middle zone of the lobule, and in advanced cases large areas may be entirely converted into amyloid; the cells first become atrophic and then wholly disappear.

In the kidney amyloid may affect the straight vessels of the pyramids or the glomerular arteries and the glomeruli. In the glomeruli it appears first in the capillary wall and finally all the vessels may be obliterated.

In the intestinal wall the infiltration often is confined to the vessels of the villi. On pouring iodine over the surface the villi appear as a brown pile.

In lymph nodes the amyloid appears first in the follicles and the entire node may be converted into it.

**LOCAL AMYLOID FORMATIONS.** In addition to the general amyloid degeneration and not associated with the causes which produce it, there may be local formations of amyloid in the tissues. The amyloid appears in the form of tumor-like swellings at the base of the tongue in the mucous membrane of larynx and trachea, and in the eyelids. It has been supposed that the amyloid here may be due to an excessive local production of chondroitin sulphuric acid. (See case of amyloid degeneration, page 267.)

**HYDROPHIC OR VACUOLAR DEGENERATION.** In this condition vacuoles filled with fluid appear in the cells, usually without other evidence of degeneration. It is seen most commonly in the cells in dropsy. It may be found in the striated muscles and in the epithelium. Occasionally filaments of fibrin may be demonstrated in the vacuoles.

**HYALIN DEGENERATION.** This includes those forms of degeneration, both in the cells and in the intercellular substances, in which hyalin masses with no distinguishing chemical characteristics

are formed. In general, these masses are homogeneous, rather refractive and have an affinity for acid stains. There probably are a number of different substances included under this head. From its physical characteristics amyloid would have been so included; it has, however, distinguishing chemical characteristics. Hyalin masses are formed, as thrombi, within blood vessels (page 63). Hyalin may appear also in walls of vessels in the same position as amyloid. Irregular hyalin masses may form on the outside of capillaries particularly those of the brain. Such masses stain with hæmatoxylin and may appear as strings of beads along the vessels. In the lymph nodes small reticular areas of hyalin may be formed about the capillaries. Fibrin in old exudations may be converted into hyalin masses. In the connective tissue, particularly in cicatrices, hyalin material may be deposited between the fibrils or the fibrils are converted into it. Occasionally fresh sections of such material gives a slight metachromatic stain with methylene blue. The hyalin in the corpora fibrosa of the ovary results from the conversion of both the cells and the intercellular substance into hyalin. A peculiar form of hyalin is due to necrosis of striated muscle and is known as *Zenker's degeneration*. In this condition the necrotic muscle substance is converted into homogeneous, highly refractive material broken into disks. In the cells hyalin appears in the form of globules, which, in some cases, stain intensely with acid fuchsin. These frequently are found in tumor cells, in the cells of the spleen, bone marrow and in the mucosa of the intestine. In the kidney, especially in connection with amyloid degeneration, the swollen epithelial cells of the proximal convoluted tubules become filled with hyalin globules; these on rupture of the cells fuse into hyalin masses which later appear in the urine as highly refractive, so-called waxy casts. The tissue of tubercles either before or after caseation may become converted into hyalin and the same is true of gummata.

**COLLOID DEGENERATION.** The term colloid is given to thick glue-like or gelatinous substances which are formed by epithelial cells and has reference solely to the physical properties of the substances. Unfortunately, the type of such substances is given by the material in the alveoli of the thyroid gland which we now know to be a substance of definite chemical composition, and has no chemical relation to other colloid substances save those formed in

the hypophysis. The retained secretion of cysts particularly of the kidney may be converted into colloid. Colloid is not deposited as an intercellular substance.

Corpora amylacea are concentric oval or circular bodies of waxy character, and should be grouped among the colloids. The name refers to the supposed relationship to amyloid shown by their reaction to stains. This staining reaction varies and is not founded on any chemical identity with amyloid. These bodies are found in the acini of the prostate in both normal and pathological conditions. They may be found also in the lungs, in the ventricles of the brain and in other situations. They represent a product of epithelial secretion and are resistant to the action of acids and alkalies.

**CALCIFICATION.** Under normal conditions the deposit of lime salts in the body takes place only in the matrix of bone. Lime is present in the blood, where it is held in solution by the colloids and carbon dioxide and exists in the form of an unstable double salt of calcium bicarbonate and dicalcium phosphate. Under pathological conditions lime salts are deposited only in tissues which are necrotic or have undergone some form of degeneration. The deposit of lime salts in such tissues is due either to the fact that in consequence of chemical changes in the tissue the lime salts can no longer be held in solution, or the degenerated tissue has a special affinity for the lime, in this respect resembling the matrix of forming bone. Arteries which have undergone degeneration are particularly prone to calcification. Lime is readily deposited in cicatricial tissue in any part of the body, but particularly in the lungs. Necrotic tissue in the body, whether in connection with organs as in infarctions, in thrombi, in caseous material, etc., or as retained exudation, readily undergoes calcification. The tendency to calcification may be increased by the addition of lime to the food, and particularly when there is absorption of lime, as in cases of osteomalacia. This is described as lime metastases and the deposits take place in the lungs, stomach and kidneys. Lime salts may enter also into combination with fatty acids when these are formed in necrosis of fat tissue, in which form they are resistant to the action of acids. Necrotic ganglion cells may become infiltrated with lime salts and completely preserve their form. Tissue which is undergoing calcification, and the calcified material as well, stains deeply with hæmatoxylin. When the calcifying tissue is treated with nitrate of silver and exposed to



the light, the silver is reduced by the phosphate of lime and appears as black silver phosphate.

**CALCULI, CONCRETIONS, INCRUSTATIONS.** Solid substances may be deposited in the cavities or canals of organs or upon their walls. In the latter position they are known as incrustations. Such deposits always take place upon or within some substance known as a nucleus or matrix which may be a group of necrotic cells, a mass of mucus, or a foreign body of any sort. Usually the dissolved substance is deposited in crystalline form, although later the crystalline structure may disappear. The crystals tend to be deposited at right angles to the surface giving a radiate structure. The deposit, moreover, usually takes place at intervals; the surface may become covered with mucin or some other substance and a new deposit on this gives in addition a concentric, laminated structure. These masses may give rise to important pathological conditions by the injury to tissues caused by their presence, and by the obstruction of canals and ducts. The most common of such substances are:

Biliary calculi may form in the gall bladder or bile ducts and usually are termed gall stones. Cholestrin forms the greater part of all gall stones and calcium salts of the bile pigments are present also. Other substances may be present in variable amounts and affect the color and other physical characteristics of the calculi.

Urinary calculi may appear in the urinary bladder, in the ureters, in the pelvis and calices of the kidney. According to the character of the urine, calculi which differ in appearance and chemical composition are produced. Uric acid calculi are the most common and characteristic. Phosphate calculi are formed as a result of decomposition in the urine, with formation of ammonia from the urea. Such calculi may form upon a uric acid calculus, this by the irritation and injury of the tissues having facilitated decomposition. Calculi of this sort may attain large size and in the kidney may completely fill the pelvis and calices. Other rare urinary calculi are formed of calcium oxylate, of xanthin and of other substances.

Pancreatic calculi are formed in the pancreatic duct and are composed of a mixture of calcium phosphate and carbonate associated with more or less organic matter.

Salivary calculi formed in the salivary ducts have the same composition as the pancreatic calculi, but contain more organic matter.

Intestinal concretions usually have a nucleus of some foreign substance or undigested particles of food. Such concretions are sometimes found in the vermiform appendix.

Preputial concretions may form beneath the unretracted prepuce by the deposit of urinary salts in the retained smegma.

Lung stones may be concretions formed in the bronchi, in which they appear as concentric laminated bodies, or may be portions of calcified lung tissue which have become separated.

Phleboliths are due to the calcification of thrombi and not infrequently are found in the vessels of the spleen.

**PIGMENTATION.** Both the normal and pathological pigments of the body can be divided into the *autochthonous*, those formed by the metabolic activity of the cells; the *hæmatogenous*, those derived from the hemoglobin of the blood; and the *extraneous*, or those introduced into the body from without.

**Autochthonous pigments.** The best known of these is the melanin which forms the coloring matter of the skin, eyes and hair. It may be increased in amount from exposure to sun in which case it may be diffusely distributed, or appear as freckles. It is increased also in pregnancy, and in chronic inflammation of the skin.

Addison's Disease is caused by destructive disease of the chromafine system, the pigment of the skin and of the mucous membrane of the mouth being greatly increased. The pigment in small brownish granules is found in the chromatophores of the corium and in the cells of the Malpighian layer. The pigment is generally supposed to be melanin.

Lipochrome is a yellow pigment probably a fat or fat compound, staining with Scharlach R, and is found in fat, in the corpus luteum, in the epithelium of the seminal vesicles, in the testicle and epididymis, and in the ganglion cells. The pigment of the heart and kidneys is of the same character and is increased in senile atrophy. In the heart the pigment is found around the nuclei and extends longitudinally in the fibre. It is seen also in chloroma.

Ochronosis is the name given to a condition in which pigment related to or identical with melanin is deposited in the cartilages, in the capsules of joints and rarely in the intima of vessels. The disease is rare and the origin of the pigment is unknown.

Malarial pigment is formed from the hæmoglobin of the blood

corpuscles by the parasite of the disease. It is intensely black and exists in the parasite in the form of small rods. It is set free when the parasite segments and is taken from the blood by the phagocytic cells of the liver and the spleen, producing the dark brown or black color of these organs seen in malaria. When large numbers of the parasites containing pigment accumulate within the capillaries of the brain cortex, they give to this a peculiar chocolate brown color. The pigment remains in the spleen for a long period after recovery from the infection.

In hæmochromatosis a dark brown or black pigment is deposited in the cells and tissues or organs, particularly in the liver and pancreas. The pigment seems to be of two sorts, one containing iron, the other iron free. It is not homogeneously distributed in the organs, but is found in association with the areas of degeneration and connective tissue increase which form a definite feature of the disease. This is the pigment seen in bronzed diabetes.

Hæmatogenous pigments. The great source of pigment in the body is the hæmoglobin of the red blood corpuscles. Hæmatin is easily separated from the globin and divides into two pigments, one, hæmatoidin, isomeric with bilirubin, the other, hæmosiderin, containing the iron component of the hæmatin. When hæmorrhage takes place in the tissues hæmosiderin is formed by the destruction of red corpuscles within phagocytic cells, and appears within cells as round or irregular brown masses which give the iron reaction. The hæmatoidin is usually carried to the liver and excreted as biliverdin. Where the hæmorrhage is large in amount and where the conditions of absorption are poor and oxygen deficient, red rhombic plates of crystalized hæmatoidin are found.

Hæmoglobin may be set free in the blood by the destruction of the red corpuscles producing the condition of hæmoglobinæmia. The hæmoglobin as methæmoglobin is excreted by the kidneys giving to the urine a characteristic, dark, smoky color. The kidneys have a peculiar dark brown color, and the hæmoglobin may be found, after staining with eosin, as beaded masses in the epithelium of the convoluted tubules, and in the form of tube casts. When the destruction of blood is slow and continuous as in pernicious anæmia, the hæmoglobin is broken up, forming hæmatoidin which is excreted in the bile, and hæmosiderin, which in the form of brown granules, giving the iron reaction, is found in the liver,

kidneys and spleen. In the liver cells these granules accumulate around the bile capillaries.

**JAUNDICE** is an accumulation of the coloring matter of the bile in the cells and tissues of the body. The liver being the only place where bile is formed, jaundice is always hepatogenous in origin, and is due to the entry of bile into the blood. The bile finds its entry into the blood in two ways; (1) in consequence of obstruction to the outflow brought about by external pressure upon the ducts or the presence within them of obstructing substances: (2) by degenerative conditions in which the anatomical relations are disturbed. In infectious diseases in which there has been increased blood destruction, jaundice may come on rapidly and is due to increased formation of bile combined with liver degeneration. The bile enters into the blood through the lymphatics, and also from the rupture of the bile capillaries into the sinusoids. The coloring matter of the bile diffuses through the tissues giving them a diffuse yellow color. It is taken up from the blood by the cells of certain tissues, as the kidneys, and appears in these as greenish yellow granules. The most intense pigmentation is found in the liver. The liver cells do not seem to contain an increased amount of pigment. The bile capillaries are dilated and filled with thick masses of pigment. Pigment in granular form, or in form resembling casts of the capillary bile ducts, is contained also in the endothelial cells of the vessels and in large phagocytic cells within the sinusoids. There is more pigment in the centre than in the periphery of the lobule. In association with the pigmentation there always is found well-marked fatty degeneration of the organs due probably to the action of the bile salts which are absorbed with the bile pigment.

**Extraneous pigments.** The most common of these is carbon. This is inhaled as dust and is deposited partly in the tissue of the lung and in part finds its way into the lymphatics and is deposited in the vessels, in the tissue about them and in the peribronchial lymph nodes. When the amount of pigment is very great, as in the lungs of coal miners, the pigment may also find its way into the blood and be deposited in the liver and spleen. By means of tattooing various insoluble pigments are introduced into the tissues; these in part remain at the place of introduction, in part are carried by the lymphatics into the adjacent lymph nodes. Silver, when taken into the body in excess, may be deposited in metallic form in the

skin, intestine, mesenteric lymph nodes and kidneys. In the latter the deposit takes place in the walls of the capillaries of the glomeruli which appear grossly as black points. In chronic lead poisoning the lead accumulates in the tissues in solution; the blue line of the gums at the edge of the teeth is due to the formation of lead sulphide by the sulphuretted hydrogen formed by decomposition around the teeth.

Other crystalline substances may be deposited in the tissues, the most conspicuous example of which is given by the needle-shaped crystals of sodium urate deposited in the cartilage, in the capsules of the joints, often in the connective tissue about them, and which give rise to marked inflammatory reactions.

## DEATH AND NECROSIS

DEATH OF THE BODY AS A WHOLE results at once from the cessation of the functions of the nervous system, or of the heart, or of the lungs. There are other organs of the body, such as alimentary canal, kidney, liver and adrenal glands, whose function is essential for life, but death does not take place immediately on the cessation of their function. In death of the individual all parts do not die at once; the muscles and nerves may react to stimulation and the function of the glands and cardiac contraction may be excited for as long as several hours after death. Certain cells, such as the epidermis, may be preserved for days or months and under proper conditions will grow.

With the cessation of life the body is subject to the unmodified action of the physical environment.

There is no further heat production after death and the body takes the temperature of the surrounding medium. This loss of heat is called *algor mortis*. The only exception to this is after death from sunstroke and from certain acute infections of the nervous system in which there may be marked production of heat for several hours after death.

Rigor mortis takes place usually within twelve hours after death; it is a contraction and hardening of the muscles due to some change in their physico-chemical relation. It begins in the muscles of the head, extends to the extremities and usually disappears in about twenty-four hours. It varies in the time of onset, in degree and duration. It is most intense and most rapid in its appearance in death preceded by active muscular exercise, for example, in death from violence. After death from slow wasting diseases, it may be slight and of short duration.

The blood, while it remains fluid, obeys the laws of gravity and settles in the most dependent parts, producing a homogeneous or mottled bluish-red discoloration called *livor mortis*. Parts of the body subject to pressure are white and bloodless. The blood later becomes laked and the diffused hæmoglobin stains the vessels and the surrounding tissue. Laking takes place more quickly under the influence of bacterial action.

The blood coagulates; this is more noticeable where it is in large masses as in the great vessels and in the heart. The character of the clot depends upon the rapidity with which coagulation takes place. It may be red when the coagulation has been so rapid that the red corpuscles have not had time to settle by gravity, or white and red when the process has been slower. Such post mortem clots can be distinguished from thrombi by their greater transparency and by the fact that they do not adhere to the walls of the vessels.

The body also loses its moisture by evaporation. Drying of the surface takes place where the epidermis is thin as on the cornea, and from areas where the epidermis is absent.

Decomposition and putrefaction of the body due to bacterial action takes place. The bacteria are present in the alimentary canal, from this they make their way into the dead tissue and various changes follow. There is an almost characteristic odor; gas may form in the organs due to the action of the *bacillus aërogenes capsulatus*. A greenish discoloration appears which is usually diffuse over the abdominal organs and in the form of lines along the vessels. The relations between tissues and tissue fluids may be altered leading to the more easy separation of tissues. The epidermis, for instance, may be removed in large flakes. The rapidity with which decomposition takes place varies, and is dependent upon many factors, such as temperature, the cause of death, etc. Ferments which were present in the body may act upon the tissues. When gastric juice is present in the stomach it may act upon the wall in the most dependent portion, producing softening and even perforation. If the gastric juice enters the lungs it may soften this tissue so that pathological conditions may be simulated.

In the microscopic examination of tissues it is important to know what post mortem changes take place in the cells. The finer details of histological structures are quickly lost in decomposition, cell outlines are obscured or broken, the nuclei either do not stain, or the chromatin swells up and the nucleus stains diffusely. Changes take place most quickly in the parenchymatous organs and particularly in the central nervous system. The muscles and connective tissue membranes preserve their characteristics much longer.

NECROSIS is local death of tissue in continuity with living tissue and subject to the action of the circulation and the tissue fluids.

Under these conditions cells undergo changes which differ from those due to post mortem decomposition. When necrosis is brought about by some agent which coagulates the tissue and prevents the action of intra- or extracellular ferments, the usual changes associated with necrosis do not occur. The epithelial cells of the stomach may be killed when carbolic acid is swallowed, but no histological change is found in them. The changes in the cells by which necrosis may be recognized affect both the nucleus and cytoplasm. Those in the nucleus are karyolysis, karyorhexis and pyknosis.

*Karyolysis* means disappearance of the nucleus by solution and diffusion of the nuclear material. *Karyorhexis* means a disturbance of the normal distribution of the chromatin in the nucleus so that it swells up into clump-like masses; or the entire nucleus may be filled with swollen homogeneous chromatin. In *pyknosis* the chromatin is converted into small irregular masses which stain intensely with basic stains and which are distributed in the cells or as detritus in the surrounding tissue fluid. Pyknosis occurs especially in leucocytes. The nuclear detritus of lymphocytes tends to take crescentic shapes. Normal granulation and all structural differentiation in the cytoplasm disappears. The cell becomes changed into a homogeneous, highly refractive mass often containing vacuoles which may contain filaments of fibrin. The necrotic cells usually are swollen, and separated from their connection with one another. The cytoplasm has an increased affinity for acid stains. The necrosis may affect areas of tissue or only certain groups of cells; in the liver, for instance, affecting the liver cells of an area leaving the endothelial cells unchanged or it may affect single liver cells irregularly distributed.

**COAGULATION NECROSIS.** Under this name a special form of necrosis has been described as a coagulation of the cytoplasm and the tissue fluids with or without the formation of fibrin. The type of this form of necrosis is seen in infarction. It is doubtful if this should be regarded as a special type of necrosis since in all necrosis coagulation of the cell contents probably takes place.

**LIQUEFACTION OF COLLIQUATION NECROSIS.** The necrotic tissue may become liquefied and form a space filled with fluid and tissue detritus. This occurs chiefly in the brain.

**FAT NECROSIS.** This is a peculiar form of necrosis which is due



to the action of the pancreatic juice on the surrounding fat tissue. This juice contains a fat-splitting ferment, which separates the fatty acids from the glycerine. The acids remain as needle-shaped crystals or combine with the lime salts to form soaps.

Certain forms of necrosis may be associated with a definite cause. In eclampsia, for instance, areas of necrosis are produced in the liver which consist in a peculiar fibrinoid change of the cells.

The causes of necrosis are manifold. The two most general causes which are met with in human pathology are disturbances in the circulation and the action of toxic substances which usually are of bacterial origin.

GANGRENE is necrosis with putrefaction. Necrosis of large external parts of the body, as an extremity, in many ways resembles general death. The changes of the cells and tissues seen in focal necrosis are not present, and the parts are subjected more to the action of certain physical changes, for example, evaporation. The most frequent cause of this necrosis is loss of blood supply by occlusion of vessels; other causes which injure tissue in mass, as the action of cold, may produce it. The putrefactive bacteria may be present in the necrotic tissue or they quickly gain access to it and putrefaction takes place. Two main forms of gangrene are distinguished. The first is dry gangrene, in which there is rapid loss of fluid by evaporation and the tissue becomes dry and black, resembling that of a mummy. In the other form, known as moist gangrene, there is a greater abundance of fluid in the part and the putrefactive processes more marked. This form of gangrene takes place in œdematous parts or when, during the process of necrosis, an exudation is formed in the tissue, or when, owing to the presence of a large amount of subcutaneous fat, evaporation is interfered with. When necrosis takes place in parts of the body where there is abundant moisture and a ready access for bacteria, as in the lung, putrefaction resulting in gangrene is likely to occur.

EXPERIMENTS. For the experimental study of degenerations, cloudy swelling and fatty degeneration are most adaptable. Cloudy swelling can be produced by injecting 0.001 gram cantharadin, dissolved in acetic ether, subcutaneously into a guinea pig daily for three days. Histological sections and salt solution suspensions of fresh scrapings from the liver and kidneys present instructive pictures. Fatty degeneration can be produced in the cat or dog by

administration, through the stomach tube, of phosphorus in olive oil in doses of 0.020 gram to the kilogram of body weight. Frozen sections and scrapings of liver can be stained with Scharlach R. and studied. The histological appearance is striking and constant.

Calcification is best produced experimentally by the ligation, aseptically and under ether anæsthesia, of the renal artery of a rabbit. Autopsy at the end of four weeks shows the organ shrunken, extensively calcified and occasionally partly ossified. Necrosis and connective tissue growth are marked and the deposition of the calcium salts in the renal tubules is clearly made out on histological examination. An additional experiment in the so-called metastatic calcification is made by the injection of 10 c.c. saturated calcium lactate solution into the peritoneal cavity of a rabbit. Stomach and lungs show the metastatic deposit of the precipitated lime.

Of great interest in pigmentation is the phagocytosis and transference of the pigment granules. Five cubic centimetres of finely divided cinnabar suspension are injected into the peritoneum and in various subcutaneous positions. Autopsy and microscopic sections twenty-four hours later show beautifully the phagocytosis and distribution of pigment in the regional lymphatic apparatus. Biliary pigmentation of the liver and other tissues can be demonstrated by the ligation of the common duct of the cat or rabbit, preferably the former. The liver shows diffuse pigmentation as well as focal accumulation of granules.

For the experimental phases of necrosis the student is referred to the effect of the ligation of the renal artery of the rabbit. A most striking example is seen in the liver of guinea pigs which have been subjected to prolonged chloroform anæsthesia. This can be done successfully by placing the animals in a box with a glass cover and forcing the chloroform vapor in by means of compressed air. An outlet is placed at the opposite end of the box to provide for the free passage of the vapor and the animals observed through the glass cover. Repetition on two or three successive days ensures the success of the experiment and if the animals are killed at different periods the rapidity of regeneration can be followed. Ether necrosis (see page 129) and specific immune serum necrosis (see page 69) will be studied later.





45 c









45 g







45 k



45 m









## INFLAMMATION

This term is used to express the sum of the changes which take place in a tissue after an injury. The changes vary both in degree and character; they are affected by the nature of the injurious agent and the intensity of its action, the kind of tissue acted upon and the variations in the resistance of the individual. Certain conditions may be recognized as essential to the process. There is always some change produced in the tissue by the injurious agent; certain disturbances in the circulation take place leading to an exudation of fluid and cells from the blood vessels; there is a new formation of cells in the part.

It may or may not be possible to demonstrate the tissue lesions produced by the injurious agent since there may be injury to cells without morphological change and shown only by abnormal reaction. The greatest degree of injury is shown by necrosis. This may affect the cells alone, or there may be combined with it destruction of the intercellular substances and coagulation of the blood and of the tissue fluids. Slight changes consisting in swelling and vacuolization of protoplasm or changes in nuclear structures may be produced. By the effect of trauma the normal relations of tissues may be disturbed, blood vessels may be ruptured and cells separated from their relations with the intercellular substances.

**THE VASCULAR PHENOMENA.** The sequence of these is best observed by the direct microscopic examination of a loop of the exposed mesentery of a curarized and pithed frog. The exposure of this tissue to the air produces a sufficient degree of injury, and the greater the care taken to avoid undue injury in making the exposure, the better will be the results. The first change seen is a slight contraction of the arteries and a diminution in the rapidity of the circulation in capillaries and veins. This is temporary, difficult to demonstrate and is followed quickly by dilatation of all the vessels and a greatly accelerated blood flow. The dilatation is most marked in the veins, less in the capillaries and least in the arteries. The axial core of red corpuscles and the plasma zone in which the white corpuscles move remains as in the normal. The

current in the dilated vessels becomes slower and the white corpuscles move relatively more slowly than the red; in consequence of which they accumulate in the capillaries and veins lining the walls of the latter. Single corpuscles temporarily cling to the walls and then are carried further by the current. Finally, numbers of white corpuscles become attached to the wall of the vessel; here they become amoeboid, and, seemingly, by amoeboid activity, pass through the walls of the vessels and appear in the tissue. As the stream becomes slower the plasma zone disappears and the corpuscles fill the vessel. The *emigration* of the leucocytes takes place chiefly in the small veins, to a less extent in the capillaries, and, under usual conditions, not at all in the arteries. The red corpuscles, though in much smaller numbers, pass through the walls of the capillaries; *diapedesis*. They become attached at one point to the capillary wall and stretch out in the current like elastic bags. A small protrusion of the corpuscle appears opposite the point of attachment and the entire corpuscle seems to pass through a minute opening in the wall, very much in the same way that partially filled elastic bags can be passed through a small opening. Not only do the corpuscles pass through the vessels, but the blood fluid passes out also. This cannot be seen, but both white and red corpuscles which have passed into the tissues are carried away from the vessels by moving currents. When fresh inflamed tissues are quickly fixed, then sectioned and stained, conditions representing every stage of the process as it occurs in the mesentery can be observed, and the emigration better studied than in the living tissue.

These conditions in the inflamed part give rise to certain phenomena, in part objective, in part subjective, which are described as the cardinal signs of inflammation. They are heat, redness, swelling and pain.

There is a subjective sense of heat and if the temperature of an inflamed area on the surface be taken it will be found hotter than a corresponding normal part. There is no formation of heat in the inflamed part, and the temperature never rises above that of the interior of the body. The heat is due to the more rapid circulation, more heat being brought to the surface from the interior by the accelerated arterial flow.

Redness is due to the presence of a greater amount of blood in the part. When the circulation is active, the color is a bright red;

when the blood stagnates in the dilated vessels, it loses its oxygen and the color is dusky and bluish.

Although a certain amount of turgor or swelling is produced by the dilatation of the vessels, this is a negligible factor as compared with the effect of the exudation. The total amount of exudation cannot be determined by the degree of swelling, there is an increased outflow through the lymphatics and the swelling represents merely the exudation which remains. The fluid distends the tissue spaces and separates the connective tissue fibres. It passes readily to surfaces, as in the lung, and may collect in serous cavities. In inflammation of the skin the exudate formed in the corium passes through the lower layers of the epidermis and elevates the impenetrable horny layer, forming blisters. In the inflamed mucous membrane it passes through the more loosely connected epithelial cells to the surface, so that swelling may not be a prominent feature. By means of the exudation, red corpuscles may be carried to surfaces and into the tissue spaces. The chemical examination of the exudate has shown that it is richer in protein than the lymph, but the salt content is the same. Usually fibrin, to a greater or less extent, is formed in the exudation. Fibrinogen is present in the exudate and fibrin ferment is provided by the disintegration of leucocytes and tissue cells. Necrotic cells in the tissue may form nodal points about which the fibrin collects. A large amount of fibrin in the exudate gives a greater degree of induration to the swelling and indicates a more severe type of inflammation. When the conditions for the production of fibrin are present in the epithelium of a mucous membrane, the exudate coming from below coagulates on the surface forming a membrane. The exudate may extend far beyond the site of injury and be found in normal tissues. The cells of the exudate form one of its most characteristic features. All the cells of the blood enter into it to a varying degree. The polynuclear leucocytes play the most important part and in certain inflammations, especially those produced by the pyogenic bacteria, may be the only cells which emigrate. When the different leucocytes take part in the exudation, the polynuclears are always the first to appear. Eosinophile cells are most numerous in the inflammations produced by animal parasites, but a few usually are present in any exudation. The mononuclear cells emigrate later than the polynuclears and rarely are present in large numbers.

Lymphocytes often are found in very large numbers, particularly in cases where the cause persists and the inflammation lasts for days. The numbers in the blood never seem sufficient to furnish the numbers in the tissue by emigration. In hardened sections they may be seen in mural arrangement within the vessels and in various stages of emigration. Blood platelets never are found in the exudation. They seem not to have the amœboid power which would allow of active emigration, nor the degree of solidity necessary for passive transmission.

The tissue changes will be described more fully under degeneration and repair.

Inflammations are divided into acute and chronic, but there is no sharp separation, the length of time the inflammation has lasted and the conditions produced serving as criteria. The best examples of acute inflammations are given in those injuries of tissue, which are produced by a cause acting temporarily, as, for example, minor degrees of heat. In the chronic inflammations the cause persists and the inflammation lasts during the continuance of the cause, or until the tissues have adapted themselves to the new environment produced. The frequent repetition of inflammation in a part may lead to chronic inflammation; the repair of the tissue after each successive injury is progressively less perfect and finally a condition of increased vulnerability is produced, in which causes, to which the normal tissues would adapt themselves, produce injury and inflammation.

Various divisions of inflammation are made depending upon the character of the exudate. *Serous inflammation* is produced by a mild degree of injury, and the exudate is almost entirely fluid. The exudate which is formed by sunburn, or by the action of mild caustics, is of this character. The fluid which collects in the blisters contains very few leucocytes and clots feebly. In *fibrinous inflammations* the exudate contains a large amount of fibrin. The amount of fibrin seems to be influenced by situation, being most abundant where the exudate passes to a surface. It also is influenced by the cause, thus inflammation produced by certain bacteria usually takes on a fibrinous character. Such an exudate combined with necrotic epithelial cells forming a membrane on a mucous surface is called *diphtheritic*. Such conditions most frequently are produced in the mucous membrane of the throat by

the action of the diphtheria bacillus but may be produced by other organisms and in other situations. *Hemorrhagic inflammation* is characterized by the presence of large numbers of red blood corpuscles in the exudate. It indicates a severe type of inflammation and the condition of the individual exerts a more important influence than in the formation of other exudations. In badly nourished individuals, especially in the cachexia of cancer, in certain diseases affecting the character of the blood or blood vessels, it is more likely to occur. The special characteristics of the *purulent exudation and abscess* will be considered with the pyogenic bacteria. *Catarrhal inflammation* is an indefinite term and indicates the increased discharge from an inflamed mucous surface. The fluid discharged is in great part the exudation of both fluid and cells which passes through the comparatively loosely connected epithelial cells. This is added to by an increased secretion from the mucous glands.

The pain of an inflamed part is attributed usually to the pressure exerted by the exudate upon the sensory nerves. Parts, such as the peritoneum, which ordinarily have but little sensation become exquisitely painful when inflamed. In general, the pain is greater when the exudation takes place in dense unyielding tissues as the periosteum. There usually is greater pain in inflammation of the corium than in the loose subcutaneous connective tissue. Certain bacterial inflammations produce more pain than the same condition due to another cause. A rapidly forming exudation in the corium in urticaria is not painful. Although the tissue pressure exerts some influence, and in certain cases, a great influence, it is not the sole factor in causing pain. In addition, there is the direct action of the injurious cause on the sensory nerves, possibly added to by the action of toxic substances formed in the inflamed part.

There is no adequate explanation for the changes seen in inflammation. They occur, the conditions for their occurrence are known and they can all be produced experimentally; but the exact nature of the primary change produced by the injury is not known nor in what way the changes act in bringing about the vascular phenomena. Various hypotheses have been advanced in explanation. The dilation is generally attributed to a change in the vessel produced either directly by the injurious agent or by the toxic substances elaborated in the injured tissues, these acting either by stimulations

of the vaso-dilators or by paralysis of the vaso-constrictors or by direct paralysis of the muscle fibres. The dilatation is seen, however, in the vessels at a distance from the injured area. The fluid exudation is attributed to the same cause, a change in the walls of the vessels whereby they become more permeable. It has been supposed also that the osmotic relations between blood and tissue fluids is altered, the osmotic pressure in the latter being raised by the formation of crystalloid substances from the molecular destruction of cells and tissue. The passage of the leucocytes through the walls usually is attributed to their amœboid activity, and the appearances are indicative of this, whether the process is directly observed or the stages studied in sections of hardened tissues. On the other hand, it is held that their passage is due to filtration, they being forced through by increased intravascular pressure. In favor of this is the fact that the non-amœboid red corpuscles pass through and also it can be shown experimentally that fat globules pass through in such conditions. When the vessels in an inflamed area are injected with silver nitrate solution, thus demonstrating the endothelial lines of junction, the emigration is seen to take place chiefly at such lines of junction. Whether or not there are actual openings, stomata, at these points through which the corpuscles pass, is uncertain. In regard to the formation of the exudation, it must be remembered that the capillary wall is a very thin membrane, probably colloidal in character, in the dilated condition much thinner than normal, and this physical change favors both filtration and osmosis. The slowing of the current in the dilated vessels may be attributed in part, at least, to increased friction of the blood; this being produced by the diminution of fluid owing to the exudation, by the opposition given by the adherent corpuscles and the hypothetical change in the walls.

The leucocytes in the exudation collect around areas of necrotic tissue and in bacterial inflammations around bacteria. When the centre of the cornea is injured the leucocytes enter the cornea at the periphery and pass to the injured area by means of the communicating corneal spaces and between the fibres. This indicates that some means of communication must exist between the injured area and the leucocytes, and there can be no other means of communication than by the action of chemical substances. This influence which chemical substances exert on the motion of living organisms



is known as *chemotaxis* or *chemotropism*. Certain substances are known to attract, others to repel, these phenomena being known, respectively, as positive and negative chemotaxis. The effect in causing motion in a certain direction is attributed to a stimulation of the leucocyte on the side toward the source of the stimulus, thus directing motion. The action of chemotactic substances affects not only the leucocytes in the tissues, but also those in the circulating blood. In the vessels outside the inflamed cornea the mural accumulation of leucocytes takes place chiefly on the side of the vessel towards the cornea. The emigration of leucocytes does not take place blindly, for in different conditions only certain leucocytes emigrate. In the copious sero-fibrinous exudation produced in the scrotum of a rabbit by freezing, mononuclear cells are found, and in most bacterial inflammation only the polynuclear cells emigrate.

If the peritoneum of an animal be inflamed by the injection of hot water and the blood be examined after the exudation has begun, the leucocytes will be found to be reduced in number depending upon the rapidity of emigration. This condition is called *hypoleucocytosis*. The number of leucocytes then slowly increases until they exceed the normal. Such an increase is known as *hyperleucocytosis* and in extensive acute inflammations in man, as in croupous pneumonia, there may be 60,000 instead of 8000 per cm. The examination of the bone marrow shows that in the beginning the leucocytes diminish in number due to their rapid passage into the blood. There then takes place a rapid new formation of leucocytes. The marrow changes its character, becoming red, there are abundant nuclear figures in the cells and the newly formed leucocytes pass into the vessels. Changes also are seen in the lymph nodes which receive the lymphatics from an inflamed area. They usually are swollen and redder than normal. On microscopic examination the lymph sinuses are found dilated and contain numerous cells, some of which represent the exudation cells which are brought to the nodes by the lymph stream, and some are newly formed. The lymph brings to the node injurious substances of various sorts which may produce necrosis or may stimulate the node to the formation of new cells.

**HEALING AND REPAIR.** The changes which have been described will continue in progress until the injurious agent is removed or the tissues have adapted themselves to its presence. The fluid exuda-

tion plays an important part in the dilution and removal of injurious chemical substances. In inflammation produced by bacteria it constantly brings to the part bactericidal or immune substances. The presence of the exudation in the tissues constitutes an abnormal condition and in the process of healing it is removed. The fluid exudation is removed from the tissues by the lymphatics and to a less extent by the blood vessels. Leucocytes and red corpuscles pass into the lymphatics and may be found in the sinuses of the adjacent lymph nodes. Many cells both white and red undoubtedly disintegrate in the tissues or are destroyed by phagocytic cells. When many red corpuscles are in the exudation, blood pigment as an indication of their destruction remains in the tissue. Fibrin cannot be absorbed, and is, in part, liquefied by a process akin to digestion. This is termed *autolysis* and is best seen in the liquefaction of the fibrinous exudation in pneumonia. The process is due to a ferment action, the ferment being provided by the polynuclear leucocytes. All cells, probably, contain such autolytic enzymes which in the living cells are held in check and become operative after the death of the cell. The liquefaction and removal of fibrin does not take place readily when the exudation is on a serous surface. It is then removed by the process of organization. In this a cellular vascular tissue grows from the adjacent living tissue and substitutes itself for the exudation which disappears as the growth advances. Such a tissue is termed *granulation tissue* and its formation is best studied in the ulcer. This is a loss of substance on a surface involving both the surface covering, and, to some extent, the underlying tissue. In the process of healing an exudation consisting of red and white cells and fibrin is formed, filling the loss and into this the granulation tissue grows as in organization. New blood vessels form from the underlying small veins and capillaries by the proliferation of the endothelial cells. The endothelial cells enlarge, the nuclei become more prominent, and they send out large pointed processes which become nucleated by nuclear division in the parent cell. Cell division and growth go on rapidly until a small mass of cells is formed, which grow into the exudation. The elongated cells become laterally disposed, communication with the old vessels is established and new vessels thus are formed. The new growing vessel always has numerous pointed protoplasmic processes at its apex. These unite with

similar processes from adjacent vessels, the vascular formation proceeds along the communication and in this way loops are formed making a circulation possible. The name "granulation tissue" is derived from the granular appearance of the surface of the ulcer, as seen by the naked eye, the granules corresponding to small masses of newly formed vessels. The new vessels are characterized by the large size of the endothelial cells, in which nuclear figures are common, and by a constant emigration of leucocytes from them. The formation of new connective tissue cells proceeds along with the new formation of blood vessels, sometimes in contact with them, sometimes between them, and intercellular fibrils appear in relation with the cells. As this tissue penetrates the fibrin the latter disappears often first becoming hyalin, and the leucocytes in part disintegrate as is shown by the nuclear detritus, and in part they are destroyed by phagocytic cells.

**PHAGOCYTOSIS.\*** Cells, bacteria and other insoluble substances may be removed by phagocytosis which essentially is an intracellular digestion. Certain cells like amoebæ take into their cytoplasm substances which come in contact with them, there being, however, in the different cells a choice as to the substances taken up. The invasion of necrotic cells and tissues by polynuclear leucocytes is not identical with phagocytosis. The leucocytes under such conditions disintegrate and probably assist in the autolysis by the liberation of enzymes. Nor can the presence of bacteria within cells always be taken as an indication that they are being destroyed by phagocytosis, since certain bacteria seem to find the optimum conditions for existence in intracellular life. The polynuclear leucocytes are generally phagocytic for bacteria, the mononuclear endothelial cells of the blood to a much less extent and the cells of the tissue probably to a very slight extent. Neither cells nor other substances than bacteria are taken up by the polynuclear leucocytes. The most generally active phagocytic cells are those produced by proliferation of tissue cells. All types of endothelial cells, those in the blood, the new cells derived from proliferation of endothelium of blood or lymphatic vessels, or the wandering endothelial cells of the tissue are phagocytic in high degree and chiefly for other cells and for various foreign bodies. Proliferating connective tissue cells are also phagocytic, but to a less degree.

\* Phagocytosis in its immunological relations will be discussed under infections.

The cells derived from proliferation of the lining cells of serous cavities form a great part of the phagocytic cells of the body, and the same is true of the closely kindred cells lining the lung alveoli. The more highly differentiated cells of the body do not become phagocytic except under certain conditions. All those tissue cells whose phagocytic powers are directed chiefly towards other cells, form the *macrophages* of Metschnikoff, the polynuclear cells are the *microphages*. Cells belonging to the lymphoid series are never phagocytic and, on the other hand, no cells, with the possible exception of the red blood corpuscles, are so generally the object of phagocytosis. Cellular digestion is carried on not only directly within the cytoplasm, but in contact with it. Phagocytic cells may join together forming a syncytial mass, or giant cell, which may enclose a foreign body or form an extensive surface contact with it. Most of the giant cells found in pathological tissues are formed in this way. Phagocytosis plays an important part in the infectious diseases and in the most varied pathological processes. In phagocytosis the family relationship is respected, cells of the same type not devouring one another; the red corpuscles and lymphoid cells are the strangers to whom hospitality usually is extended.

**REPAIR.** The removal of the exudate is but one of the steps in repair. Any injury or destruction of tissue must be made good by the activity of the tissue cells. The leucocytes of the exudation take no part in tissue regeneration. In the tissues there are cells intimately associated with this, as the endothelium of blood and lymph vessels, the connective tissue cells, the nerves and differentiated epithelial structures, and cells which are present in variable numbers and do not form an essential part of the tissue, as the wandering polynuclear leucocytes and endothelial cells and the various lymphoid cells. The tissue polynuclear cells need not be considered; whatever their function is, they take no more part in repair than do the polynuclear cells in the exudate. Injury or destruction of simple covering epithelium is made good quickly by new formation of epithelium or by the recovery of cells slightly injured. How great a degree of injury cells can sustain and recover is uncertain. The epithelium lining serous cavities and the lining epithelium of the lung alveoli has great power of proliferation, quickly covers over defects and produces free phagocytic cells. In certain cases there is marked proliferation of the endothelial cells.

These may form a thick cellular lining in the larger vessels, emigrate and contribute to the phagocytic cells of the tissue. In vessels of capillary character large numbers of endothelial cells are formed and these in the vicinity of the vessels may appear as branched cells not unlike fibroblasts. The function of these endothelial cells, apart from the part they play in phagocytosis, is unknown. It cannot be shown that they form intercellular substances. There is a great departure in the size and form of such endothelial cells from those represented in the endothelial cells of the blood, but the transitional stages can be seen. The lymphocytes in the healing tissue appear as small lymphocytes and as plasma cells. In certain forms of chronic inflammation, both simple and infectious, *plasma cells* may be present in enormous numbers very frequently as masses around the vessels. They usually are oval, the long diameter  $7-9\mu$ , the short  $5-7\mu$ , but the size and shape varies. The outline usually is smooth, but blunt processes indicative of amoeboid movement are often seen. The cytoplasm is dense, without evident granulation and stains strongly with basic dyes. The nucleus is round and is eccentrically placed in the cell. It has the characteristics of the lymphocyte nucleus, but stains more deeply and has more and larger clumps of chromatin. In the larger cells two or more nuclei often are seen. The cells are capable of proliferation and nuclear figures are found in them. The source of these cells is uncertain. Transitions between them and the small lymphocytes can be seen and they appear, in part at least, to develop from these. The part they play in the process of tissue repair is not known.

Repair of the connective tissue takes place by a new formation of connective tissue cells and intercellular substance. The connective tissue cells become swollen, basophilic, stellate in shape, or have long, widely extended, branching processes. The nucleus swells, usually is oval in shape and the chromatin is increased. Nuclear figures may be seen in these cells as early as eighteen hours after the injury. In the injured cornea the extension of the new cells into the area of injury takes place much in the same way that new blood vessels are formed. A long process is given off from a cell and the nuclei resulting from the division of the parent nucleus move up into the process and the cytoplasm increases around each new nucleus, forming new branched cells. In the organizing exudate the

new cells seem to move along such supporting tissue as the newly formed blood vessels. It is not uncommon to find cell fragments which retain the characteristics of the cytoplasm given off from both polynuclear and plasma cells, and such fragments, and even entire cells, are taken up in the growing fibroblasts. It is not possible to arrive at any conclusion as to the manner in which the intercellular substances are formed from the cells. The fibres appear between the cells and cell processes seem to pass into fibrils. Two sorts of fibrils appear, the ordinary small fibrils of the white fibrous tissue and large fibrils which have the same relation to the cells as the fibrils of smooth muscle. This process is almost invariably accompanied by a new formation of vessels, which takes place as described in organization. The extent of the connective tissue formation and its character depends upon the degree of injury. In a simple, clean, incised wound of the skin which is brought closely together, a very small amount of exudation containing little fibrin and few leucocytes is formed between the opposing surfaces. The adjoining connective tissue cells proliferate to a slight extent and give rise to a minimum amount of intercellular substance which forms the permanent union. In the case of large loss of substance, as in an ulcer or in chronic inflammation about a persistent cause, such as a foreign body, the new formation may be much greater and differs in character from that formed in the simple incision. The coarse fibrils are formed to a much greater extent, and all the fibrils seem to fuse together, forming dense masses; the newly formed blood vessels in great part disappear leaving the tissue anæmic; most of the cells also disappear, leaving the tissue less cellular than normal. There results a hard white tissue, the *cicatricial tissue* or *scar*, which, both to the naked eye and microscopically, is sharply differentiated, and which has a marked tendency continually to contract.

**SUMMARY.** An injury to tissue is followed by increased afflux of blood and by exudation. In the process of recovery the fluid exudate is removed by lymphatic and blood absorption. The cells of the exudate in part pass into lymphatics and are removed, in part undergo autolysis or are taken up by phagocytic cells, or they may collect into dense masses which after necrosis become calcified or they may undergo organization. Cysts may be formed by absorption and partial organization of the necrotic tissue and exudate.

Fibrin in the exudate may be dissolved by the action of enzymes given off by the leucocytes, or newly formed connective tissue may grow into and replace it. The processes of repair take place from the tissue cells, the cells of the exudate taking no part in it. Repair of the injury is rarely perfect; in the place of the injured tissue scar tissue is substituted, which is more vulnerable to subsequent injury and less perfect in function.

**EXPERIMENTS.** The experiments possible on the subject of inflammation are so numerous and varied that only a relatively small group can be performed. Most important seem to be those connected with the processes of exudation, phagocytosis and repair. In the first group are included the study of the rabbit's ear after exposure to water at  $53^{\circ}\text{C}$ . for three minutes. Both this and a similar study of the rabbit's ear rubbed with croton oil give the cardinal symptoms of inflammation. The same experiments should be performed on rabbits whose cervical sympathetic has been divided in the neck.

The production of leucocytic exudate in the rabbit's pleura by the injection of a few cubic centimeters aleuronat suspension, of a purulent exudate by the injection of 1 c.c. bouillon culture bacillus coli communis or staphylococcus pyogenes aureus, and the production of a sero-fibrinous exudate by means of the injection into the pleura of 2 c.c. turpentine, gives opportunity for the study of exudates and of the different etiological relations of the exudate. The localized abscess can be produced by the subcutaneous injection of a fresh culture of staphylococcus aureus or colon bacillus, and the metastatic abscesses of kidney and heart produced by injection of 1 c.c. twenty-four-hour bouillon culture of staphylococcus aureus into the posterior auricular vein of the rabbit. Both these experiments should include careful microscopical examination of the pus and of the diseased tissues.

For the study of phagocytosis reference to the experiment in pigmentation (see page 45) is important for the demonstration of phagocytosis of mineral inert particles. For the study of phagocytosis of animal cells 3 c.c. of a mixture of equal parts salt solution and defibrinated pigeon's blood should be injected into the peritoneal cavity of a guinea pig. Intracellular inclusion, vacuole formation and digestion can be studied by withdrawing some of the material in the peritoneum by means of a drawn out capillary

pipette at the end of one, two and three days, making spreads and staining with Wright's stain. A similar experiment, using a bouillon culture of colon bacillus and withdrawing the exudate at six, twelve and twenty-four hours shows the phagocytosis of bacteria. Most important is the influence of opsonins on phagocytosis. This is well illustrated by following these brief directions: Into a 7 by 75 mm. test tube two-thirds filled with 1 per cent sodium citrate solution drop twenty drops human blood (fellow student), centrifuge and collect the leucocytes in a warm drawn out glass pipette. Collect a small amount of blood in a Wright tube, allow to clot, centrifuge and collect serum. Make a salt solution suspension (5 c.c.) of a twenty-four-hour slant agar culture of *staphylococcus pyogenes aureus*. Draw out several glass pipettes of approximately uniform diameter and make a point with a blue pencil. Fill to mark with leucocyte suspension, permit some air to run in, then to mark with bacterial suspension, then more air, then to mark with salt solution. Expel into a sterile Petri dish, mix and allow to run into pipette again. Repeat, using a fresh tube and serum instead of salt solution. Incubate the tubes twenty minutes, make spreads, stain with Wright's stain and note the difference produced by the opsonins in the serum.

For the study of repair three experiments may be chosen. After removing the hair from two areas in the opposite flanks of a guinea pig, the areas should be washed, the animal anæsthetized and a linear wound made in each area. Into one an agar culture colon bacillus should be rubbed, the other to be kept clean. The delay of repair in the infected area usually is striking. Repair in a more complicated structure can be observed by fracturing the livers of six guinea pigs, under complete ether anæsthesia, then killing one on alternate days and studying in sections the sequence of changes. Repair in a nonvascular structure can be studied by making, under deep ether anæsthesia, a linear wound in the cornea of a rabbit. The repair is rapid and instructive pictures can be obtained by making sections of the cornea at the end of two days.







59 c





















59 m









## THE PATHOLOGY OF THE BLOOD.

In a consideration of the pathology of the blood and circulation certain normal conditions must be borne in mind. The blood differs from the other tissues of the body in having a fluid intercellular substance and in the persistence of embryonic processes of cell formation. The blood has great power of cell regeneration, and cell equilibrium although easily disturbed, is rapidly re-established. The intercellular fluid is complex in its composition, for the blood is the general carrier and intermediary agent for all the tissues. The circulation of the blood is maintained by the pumping action of the heart and the contractility of the arteries. The sectional area of the blood vessels gradually increases from the aorta to the capillaries reaching in the latter an area 800 times greater than that of the aorta and from this decreases again towards the heart. The blood pressure diminishes from the aorta to the venæ cavæ; the general estimate of pressure being 110 mm. of mercury in the radial artery, 20 mm. of mercury in the capillaries, zero and indistinctly negative, at the entrance of the venæ cavæ into the heart. The blood supply of an individual organ depends upon the blood pressure, the calibre of the supplying artery, the latter being regulated by the action of the vasomotor nerves on the muscle cells of the media and the venous outflow. Not only has the blood great regenerative capacity, but throughout the circulation there is a remarkable power of adaptability to pathological conditions. This is effected by changes in the blood itself, by changes in the contractile force of the heart, by changes in the calibre of the arteries and by changes in the reciprocal relations between the blood and the tissue fluids. The blood pressure is the main factor in the production and maintenance of the tissue pressure, which in turn results from the interrelation of capillary pressure and the elasticity of the skin and other tissues.

*Anæmia*, although meaning literally absence of blood, is used to express a diminution in blood quantity (*oligæmia*), and a diminution in the number of corpuscles (*oligocythæmia*). The general estimate

of the amount of blood in the body varies from 5 to 7 per cent of the body weight, and loss of blood up to 3 per cent of the body weight is not necessarily fatal. After a considerable loss of blood there is a rapid fall in blood pressure which in non-fatal cases is restored by the withdrawal of tissue fluid into the blood, and finally by regeneration of the corpuscles in the blood-forming organs. After death from hæmorrhage the surface is pale, the tissues are lax and relatively dry from the absorption of tissue fluids. The pallor of the organs shows how much their natural color depends upon their blood content. All the appearances of anæmia may be produced by diminution in the number of red corpuscles.

Under normal conditions there is constant destruction of the red corpuscles, as proven by the constant formation of bile pigments from hæmoglobin. Where and how the destruction is effected and the length of life of the corpuscle is uncertain. Estimates of the amount of bile pigment produced daily show that a daily consumption of one-tenth of the total hæmoglobin of the corpuscles is required for the process, which by computation makes the average life of the corpuscles approximately ten days.

There are two well recognized forms of anæmia. In one, *pernicious anæmia*, there is an increased and continuous destruction of the red corpuscles which may be reduced to less than 1,000,000 per cmm. No free hæmoglobin is found in the blood and the hæmoglobin content of the corpuscles is increased. There is a peculiar pale lemon tint to the skin, and examination of the blood during life shows the presence of nucleated corpuscles and variations in form and in staining reactions. The parenchymatous organs show intense fatty degeneration and red marrow fills shafts of the long bones. This contains large numbers of nucleated red cells and their antecedents. The spleen also can partake in this blood formation and may contain nucleated red blood corpuscles and a variable amount of erythroblastic marrow tissue. Very characteristic changes are found in the liver consisting in the presence of an iron-containing pigment surrounding the intra- and intercellular bile capillaries. It is generally supposed that the cause of the disease is the formation in the body of some chemical substance which is toxic to the red corpuscles and that the changes in the marrow and spleen are secondary and regenerative in character.

Closely allied to this form of anæmia is the *secondary anæmia*

which may result from hæmorrhage, from prolonged suppuration, other infections and from other exhausting conditions. The changes in the bone marrow are not so marked and the normal amount of red marrow may not be increased.

**HÆMOLYSIS.** The red corpuscles contain a considerable amount of lecithin and cholestrin which are believed to have their chief importance in affecting the permeability of the corpuscle. In hemolysis the hæmoglobin escapes from the corpuscles, is dissolved in the serum and the blood becomes transparent or laked. This laking of the blood, or hæmolysis, may be produced by lowering the osmotic pressure of the plasma or by the action of a number of hæmolytic agents. Some of these probably act by uniting with the lipid elements of the corpuscle. The discharge of the hæmoglobin into the blood plasma is called *hæmoglobinæmia*; the hæmoglobin is in the form of méthæmoglobin and is excreted by the kidneys, giving to these a peculiar brownish red appearance, and producing *hæmoglobinuria*.

By *plethora* is understood increase in the total quantity of the blood without change in composition. Plethora cannot be experimentally produced in animals by the transfusion of blood, the excess being quickly removed by blood destruction. In *hydræmic plethora* the blood plasma alone is increased in amount. Large amount of salt solution can be injected into the blood of animals but is rapidly removed by excretion. In man the condition may be produced by long standing venous obstruction when combined with diminished output of fluid. In *hydræmia* there is a relative increase in the blood plasma without increase in the total blood. The condition occurs in certain cachexic states. In *anhydræmia* there is the opposite condition of a relative diminution in blood plasma; this occurs particularly in cases of cholera, the blood being drained of fluid by the continuous exudation into the intestinal canal.

**COAGULATION.** One of the most remarkable properties of the blood is that after removal from the vessels, it becomes solid or semi-solid by reason of fibrin formation. Clotting is due to the interaction of fibrinogen calcium salts and thrombin to form fibrin.

**THROMBOSIS.** The formation during life, and from the constituents of the blood, of solid masses within the blood vessels is

called thrombosis, and the masses so formed are called *thrombi*. Though in most cases the process closely resembles the coagulation of the blood, there are many points of difference. Thrombi are always adherent to the wall of the vessel at some point, and as compared with post mortem clots they are not so elastic. Thrombi may be formed in any part of the circulation, but are much more common in the veins than in the arteries. In the heart they are more common in the right side than in the left, and in the auricles than in the ventricles. Anatomically, two sorts of thrombi may be recognized, the *red* and *white* thrombus. The red are formed of fibrin and red and white corpuscles. The clot presents much the same appearance as an extravascular clot, but the white corpuscles are in greater excess and the red corpuscles and fibrin are not homogeneously distributed. The white thrombi are, for the most part, composed of masses of blood platelets and fibrin. If an opening be made in a small superficial vein of an animal, the escape of blood shortly ceases and examination shows the vessel closed by masses of blood platelets adhering to the edges of the opening and extending as a plug into the tissue. No fibrin is demonstrable. If a vessel be exposed and injured the blood platelets collect at the site of injury and may form a mass occluding the vessel. Sections of large recently formed thrombi have much the same composition; the masses of blood platelets form a network in the meshes of which a variable amount of fibrin and corpuscles are found. The fibrin often forms immediately around the blood plates. The meshwork arrangement of blood plates probably is due to contraction, for in the forming thrombus they are homogeneously distributed. In small vessels thrombi, not completely occluding, are sometimes seen, which are composed chiefly of leucocytes and fibrin. The older the thrombi, the greater are the number of leucocytes and the amount of fibrin, and the blood platelets break up to form granular masses. Mixed thrombi composed of portions of white and red may be found, and often are due to the entry of blood into fissures of a white thrombus. A special variety of thrombus is called the *hyalin* thrombus. It is seen most frequently in the capillaries of the glomeruli of the kidneys and forms a constant lesion in death from plague. It may be produced experimentally in the kidneys of guinea pigs and rabbits by infection with the *diplococcus pneumoniae*. The hyalin

masses in the capillaries are due to the fusion of red corpuscles. In these cases the capillaries elsewhere in the body may be entirely free from thrombi. In the post mortem examination of the tissues, masses of fibrin and leucocytes often are found in the small vessels, particularly in the lungs and it is difficult to determine whether they are thrombi or post mortem clots.

A thrombus once formed may be the starting point of a continued, or propagating, thrombus which extends along the thrombosed vessel chiefly in the direction of the current and into communicating vessels. Such thrombi often show an alternation of red and white; after the formation of the primary white occluding thrombus a red thrombus forms in the stagnating blood stream and extends up to the point of entrance of the next vessel, where a white thrombus forms from the circulating blood and on this, when the vessel is finally occluded, another red thrombus is formed. Thrombi which do not occlude the lumen of the vessel are called mural thrombi. Thrombi are always rich in thrombin and it is difficult to understand why the blood flowing over a mural thrombus does not further coagulate. It is held that the coagulation of the blood within the blood vessels during life is prevented by the presence of an antithrombin, which by combining with prothrombin, prevents the formation of thrombin and it is not unlikely that the coagulation on a mural thrombus may be prevented by some such action. The endothelium rapidly grows over such a thrombus and when this takes place the further formation is prevented.

The thrombus when first formed is moist and soft in consistency. By contraction and extrusion of serum it becomes more compact, drier and more granular in texture. The interior of large thrombi, especially those formed in the heart, often undergoes autolysis and contains an opaque fluid resembling pus. This, the *puriform* softening, is to be distinguished from the true *purulent* softening which takes place when the thrombus is infected during formation or when infection extends into the thrombus from an infected area in the vicinity. *Organization* of the thrombus takes place in the same way that a fibrinous exudation on the pleura becomes organized. New blood vessels from the vasa vasorum or from the vessels of the adjoining tissue grow into it, forming a network, and new connective tissue cells are formed which follow the ingrowing blood vessels. When the thrombus ceases to extend it is rapidly

covered by endothelium, and from this new blood vessels may be formed which extend into the thrombus and form communications with the vessels which enter it laterally. In this way a circulation is established through the thrombus, which at first is tortuous, but later the vessels become straighter and then dilated both from the pressure of the blood within them and from the contraction of the connective tissue around them. This is called *canalization* and the thrombus finally may be represented by a few fibrous bands across the vessel. In other cases the thrombus may become calcified by the deposit of lime salts.

The cause of thrombus formation is imperfectly understood. The two causes which are of the most importance are injury to the endothelium and slowness of the circulation. The frequent formation of thrombi in the course of infectious diseases, and the demonstration of bacteria in such thrombi shows that infection plays a prominent part in the production of endothelial injury. The importance of the interaction of the two conditions of endothelial injury and slowness of circulation acting together is seen in the relative frequency of thrombi in veins as compared with arteries. In arteries it is not at all uncommon to find areas in which the endothelium is completely destroyed, and replaced by an uneven tissue with projecting calcareous masses and yet thrombi usually are absent. Infection takes place more easily in the veins than in the swift current of the arteries, and slow circulation also favors thrombosis. Thrombi are especially likely to form in the pockets behind the valves, in which stagnation of the blood easily takes place. In the heart, thrombi are more likely to form in the auricular appendages and between the muscular bands at the apices of the ventricles. Slowness rather than complete cessation of the current favors thrombosis. Parts of a vessel may be cut out and replaced by devitalized vessels and thrombosis will not take place, provided there is no stagnation of the current. Thrombi are more frequent in cases of chronic passive congestion than when the circulation is normal; they are particularly apt to occur in venous plexuses, as at the base of the bladder.

The results of thrombosis depend chiefly upon the size and character of the occluded vessel. The immediate effect in veins must be congestion in the distal veins and capillaries. There are usually collaterals which dilate sufficiently to carry the blood

from the congested area. The slow formation of a thrombus is favorable in that time is given for the gradual dilatation of the collateral channels. The renal vein may be occluded by a thrombus with but little impairment of the circulation. When the collateral circulation is not sufficient there may be chronic congestion and oedema in the territory which the vein drains.

**EMBOLISM** is the impaction in some part of the vascular system of any abnormal material brought there by the blood current; the impacted material is an embolus. Such emboli may be of solid, liquid or gaseous substances. Unless some distinguishing epithet is used an embolus is understood to be a detached thrombus or part of it. In the various changes which thrombi undergo the whole thrombus or portions of it can become detached and enter into the blood current. Emboli are carried along in the current until the channel (usually arterial) becomes too small to permit their further passage. Emboli in the lungs come from the systemic veins, the right heart, or pulmonary artery; those in the liver from the trunk, or branches, of the portal vein; those in the systemic arteries from the pulmonary vein, the left heart or some artery between the heart and the location of the embolus. The course of an embolus is determined by purely mechanical factors, of which the most important are the size, form and weight of the plug, the direction, volume, energy of the carrying blood stream, the size of the branches and the angles at which they are given off. Emboli coming from a source in the left heart are carried more frequently into the abdominal aorta and its branches, than into the carotid or subclavian arteries. In rare cases in which a congenital opening exists between the two cavities of the heart an embolus from a systemic vein can pass directly into the systemic arterial circulation, *paradoxical emboli*. Secondary thrombi may form around emboli.

Various results follow embolism. The occlusion by a bland embolus of an artery with abundant anastomoses, as in the voluntary muscles, the skin, the uterus, causes no obvious disturbance in circulation. Sudden death may result from the occlusion of the trunk or one of the main divisions of the pulmonary artery, or of any artery furnishing the main blood supply of an organ essential for life. The first effect of the occlusion of an artery supplying a part is a fall in pressure in all the vessels, arteries, capillaries and veins, in the part supplied. If there is an anastomosing artery the

blood of this artery will flow with greater rapidity into the area of lessened capillary pressure and in time the anastomosing artery becomes so dilated as to furnish, with the increased rapidity of stream, a sufficient amount of blood. The occlusion of small arteries rarely is disturbing owing to the abundance of capillary anastomoses which can furnish enough blood to re-establish the circulation. When, however, the occluded artery belongs to the system of so-called terminal arteries, which are arteries supplying definite regions and without rich anastomoses, the part undergoes certain changes which result in *infarction*. In the area which is undergoing infarction there is a fall in pressure; and from all the anastomoses, blood flows into the part producing intense congestion, but the capillary pressure does not rise to a sufficient height to provide for the venous outflow. Necrosis of the tissue takes place and there is abundant hæmorrhage from the distended vessels. The infarcted area usually is conical or wedge-shaped, the base being at the periphery. When the infarct is recent the area is dark red, swollen and relatively dry. It may remain in this condition, in which it is called a red infarct, but in certain organs, notably in the spleen and kidney, the centre of the infarct loses its color by the hæmolysis of the red corpuscles and diffusion of the hæmoglobin and becomes of a pale pink and later a yellowish white color. Around the white centre is a red area in which the vessels are dilated and the corpuscles in the tissue preserve their hæmoglobin. Leucocytes migrate from the adjoining vessels and make their way for a certain distance into the necrosed area. In certain parts of the body, as in the brain, the tissue becomes necrotic, and rapidly undergoes liquefaction. In the liver, due to the double blood supply and the abundant capillary anastomosis, infarction rarely takes place as the result of embolism in either the portal veins or in the hepatic artery. In the lung under normal conditions of the circulation infarction does not follow occlusion of small branches of the pulmonary artery. This is due mainly to the enormous extent of the capillary anastomosis which brings sufficient blood into the part to establish the circulation. In case, however, there is passive congestion with an increased pressure in the pulmonary veins, the circulation by capillary anastomosis is not sufficient to overcome the venous pressure and infarction takes place. Whether or not infarction takes place must depend in part upon the character of



the tissue and its resistance to lack of blood supply. If the tissue be one which easily undergoes necrosis the rapid occurrence of this will bring about the conditions for infarction before there is time for the establishment of the collateral circulation.

**PARENCHYMATOUS EMBOLI** are due to the entry of cells of organs into the circulation. This has been described more frequently in connection with the cells of the liver than of any other organ. In consequence of severe crushing injuries of the liver, portions of tissue may be forced into the hepatic veins and be carried away as emboli. The large cells of the bone not infrequently enter into the blood and may be found as emboli in the capillaries of the lung. It more commonly occurs in children than in adults. Almost invariably, in cases of pregnancy, the syncytial giant cells in the placental sinuses enter the circulation and occlude without harm, small vessels in the lungs. The cells of malignant tumors often enter the circulation and may be carried into various places producing metastases.

**FAT EMBOLISM.** At the temperature of the body fat is fluid and in case of injury, particularly crushing injuries, in which both fat cells and veins are ruptured the fluid fat may enter into the circulation. This most readily takes place in such injuries of bones. The fat then is carried into and obstructs the capillaries of the lungs. When a large amount enters the circulation it may pass through the lung capillaries and enter into the systemic circulation where it is most often found in the vessels of the glomeruli of the kidneys. The importance of fat embolism formerly was greatly overrated. With the abundant capillary anastomosis in all organs, many capillaries may be obstructed with little harm. Death may follow when the process is very extensive and great numbers of capillaries in the lungs and brain become occluded.

**AIR EMBOLISM.** When air in a considerable amount enters suddenly into the circulation it may obstruct it by forming emboli in the capillaries and by interference with the action of the heart. Cases of sudden death have been attributed to this and the presence of gas in the vessels after death was considered evidence of the entrance of air. Since it has become known that the presence of gas in the vessels is almost invariably due to the action of the *bacillus aërogenes capsulatus* or to the surgical opening of large veins in the area of negative pressure these cases have become very infrequent.

**EXPERIMENTS.** In the experimental work on blood, particular attention should be given to the study of human blood. The students can do this best working in pairs. The finger tip or ear lobule should be cleansed with soap and water, followed by alcohol and dried with a clean pledget of gauze or cotton. A puncture about 5 mm. deep should be made with a blood lancet, needle or a single point of a steel pen. A drop may be placed on a warm slide, covered with a coverslip and studied fresh to observe the natural form of the corpuscles, the rouleaux and the amœboid activity of the leukocytes. For making stained specimens two carefully cleaned coverslips are used. A small drop of blood is placed on one and the other dropped on it so that the corners remain free for grasping. As soon as the drop of blood spreads out the upper cover is rapidly slid off the lower, the two dried and stained, either with eosin methylene blue or some of the combined stains such as the Wright, Leishmann or Romanowsky stains.

For the study of some especial phases of blood destruction, anæmia and hæmatogenous jaundice, the following experiments are of value. The hæmolytic effect of the intravenous injection into a rabbit of a solution of 0.001 gram dried rattlesnake venom in salt solution. Place the animal in a metabolism cage, note the hæmoglobinuria and at autopsy study the hæmoglobinaemia and the general tissue changes. In contrast the subcutaneous injection of 0.001 gram cantharadin in acetic ether produces, in the rabbit, hæmaturia and somewhat different tissue changes, especially in the kidney. Blood destruction, hæmaglobinuria and jaundice can be produced by the intravenous injection of a specific immune serum. This is done in the cat, usually in amounts of 0.5 c.c. immune serum to the kilo of body weight. Autopsy at the end of two or three days should include careful examination of the spleen and lymph nodes for phagocytosis of destroyed blood corpuscles, of the liver for focal necrosis and of the kidneys for nephritis. A similar experiment in the recently splenectomized animal shows the most marked phagocytosis of red blood cells in the lymph nodes.

Hæmolysis *in vitro* can be determined as follows: Place in each of 4 test tubes 1 c.c. 5 per cent suspension cat's erythrocytes in salt solution. Add to test tube 1, 2 c.c. salt solution; to test tube 2, 0.1 c.c. guinea pig serum (complement) and 1.9 c.c. salt solution;

to test tube 3, 1 c.c. dilution of specific immune serum (amboceptor) which has been inactivated by a temperature of 56° C. for one-half hour; and to test tube 4, 0.1 c.c. complement, 0.9 c.c. salt solution, and 1 c.c. amboceptor dilution. Incubate for one hour at 37° C. and note that the presence of both amboceptor and complement is necessary for hæmolysis.



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## THE PATHOLOGICAL ANATOMY OF THE HEART AND THE BLOOD VESSELS

THE HEART may be regarded as a greatly modified blood vessel of the arterial type, the endocardium corresponding to the intima, the myocardium to the media and the epicardium to the adventitia. The endocardium, lined with the endothelial cells common to the vascular tube, is a non-vascular connective tissue membrane which contains a varying but small amount of elastic tissue and non-striated muscle cells. The valves are duplicatures of the endocardium with marked development of elastic fibres and with a considerable amount of nonstriated muscle. The myocardium is composed of short cylindrical, striated muscle cells arranged in bundles. The cells branch to a varying degree. The branches of different cells anastomose and vary in size, the largest being found in the ventricles. Each cell contains in the centre an oval vesicular nucleus surrounded by a small amount of sarcoplasm, which usually contains a small amount of brown pigment greatly increased in certain atrophic conditions. The epicardium is composed of connective tissue and elastic fibres and its surface is covered with flat mesothelial cells. The larger branches of the coronary arteries ramify in the epicardium. Fat tissue in varying amount occurs beneath the epicardium, especially on the right side of the heart and at the junction of auricles and ventricles. The heart is enclosed completely in the pericardial sac, the latter being attached around the great vessels. The parietal pericardium, although thicker, has the same general structure as the epicardium. The parietal pericardium has an abundant blood supply and is in close topographical relation with the pleuræ the mediastina and the peritoneum. Unlike other blood vessels the inner surface of the heart is irregular; the surface in contact with the blood is very large. The myocardium receives a large blood supply from the two coronary arteries. There is limited anastomosis between the different arterial branches, the extent varying greatly in different individuals. The capillary circulation in the myocardium is



greater than in any other muscular tissue of the body. The size of the heart varies considerably, being influenced by age, sex, height, muscular development and occupation of the individual. The average weights are 20 grams in the newborn, 300 grams between ages of thirty and fifty years, increasing to 330 grams at the age of sixty-five; the weight of the heart of the female from five years of age and upward is somewhat less, averaging between the ages of twenty and fifty years, 270 grams.

**PERICARDIUM.** The most common pathological condition is acute pericarditis, due either to an extension of infection from the neighboring tissues or to infectious organisms carried by the blood or lymphatic vessels.

The exudation may be serous, sero-fibrinous, purulent, fibrino-purulent or hemorrhagic, depending essentially upon the character of the infectious agent. Fibrin almost invariably is present, both as masses in the fluid exudate and as a deposit on the surface. In small amounts it may produce merely a clouding of the surface; when abundant it forms shaggy masses covering both parietal and visceral pericardium and often presents peculiar rolls and a network due to the friction of the opposing surfaces. The amount of the fluid exudation may be very considerable, occasionally reaching 1000 c.c. Usually healing takes place by organization of the exudate with obliteration, either partial or complete, of the pericardial cavity by the union of the opposed surfaces. Where the exudation has been very extensive, thick masses of dense cicatricial tissue may result from the organization. In association with the pericarditis there may be pleuritis with obliteration of the pleural cavities and inflammation of mediastina resulting in formation of dense masses of connective tissue. The special forms of pericarditis due to special infectious agents will be considered under the infections. Small circumscribed hæmorrhages (ecchymoses) in the pericardial tissue, especially in the epicardium, are found in death from suffocation, in various intoxications and in many of the infectious diseases. In inflammation also, especially when the exudation has a hæmorrhagic character, small epicardial hæmorrhages often are seen. Extensive hæmorrhage into the pericardial cavity, apart from that resulting from perforating wounds of the heart, is due to rupture of the heart or the great vessels often preceded by aneurysm formation. There may be large accumulation

of serous fluid in the pericardial cavity (hydropericardium), due to disturbances in the circulation.

**MYOCARDIUM.** Various forms of degeneration occur in the myocardium. Cloudy swelling occurs in most of the acute infectious diseases, especially when accompanied by high fever. Fatty degeneration is common and may not produce any macroscopic changes. It rarely is diffuse affecting equally all parts of the heart, but usually is more marked beneath the endocardium, especially in the left ventricle and in the papillary muscles, than elsewhere. Fat infiltration of the heart may be a pathological condition due to growth of the epicardial fat into the myocardium, pushing the muscle fibres aside and producing atrophy. Necrosis usually is the result of interference with the coronary circulation, or takes place around bacterial emboli. Rarely, a form of hyalin degeneration and necrosis of single fibres is seen in infectious diseases as the result of toxin action. A peculiar form of degeneration, consisting in destruction of the fibrillæ in the centre of the fibre, sometimes is seen in diphtheria and in fibres which have become hypertrophied. Extensive lesions are produced in the heart by impairment in the blood supply, due to lesions of the coronary arteries. The lumina of the chief stems or their branches may be obstructed by arteriosclerosis, thrombosis or embolism. Necrosis may result, sometimes followed by softening and perforation of the heart and more rarely by hæmorrhagic infarction. The descending branch of the left coronary artery is most frequently affected. Although the myocardium must be regarded as relatively susceptible to the action of toxic substances, as shown by the frequency of degenerations, acute bacterial infections are comparatively rare. These may be produced by infection from the blood stream or by the extension of an endocardial infection. Small abscesses may occur in staphylococcus aureus septicæmia and miliary tubercles are rarely found. Focal accumulations of cells belonging to the lymphoid type may be found in the acute infectious diseases particularly in acute rheumatic fever.

The minor degrees of the various degenerations of the myocardium may be recovered from, leaving no trace. In necrosis and the more serious injuries the degenerated fibres are absorbed and substituted by the formation of connective tissue.

**FIBROUS MYOCARDITIS**, like the degenerations, may be focal

affecting only small areas of the heart, or the entire myocardium may contain numbers of small cicatricial streaks. The substituted connective tissue has not the resistance of the muscular tissue and the area affected may gradually give way before the blood pressure and a local dilatation or aneurysm of the heart wall may result. Corresponding to the frequency of disease of the descending branch of the left coronary, the most extensive areas of fibrous myocarditis, followed by dilatation, are found at the apex of the left ventricle. In and around the areas of fibrous myocarditis, both greatly atrophied and greatly hypertrophied, muscle fibres may be seen. Parts of the myocardium which are of especial functional importance may be affected, such as the fibre bundle of His, with a resulting impairment of the association of auricular and ventricular contraction.

**HEART HYPERTROPHY.** The heart, like the other muscles and organs of the body, has great reserve force, by reason of which it is enabled suddenly to perform more work than ordinarily is called for. When there is a frequently repeated or permanent demand for increased function made upon the heart, the muscle hypertrophies. Hypertrophy is due most frequently to obstruction of the valvular orifices and affects the part of the heart concerned in forcing the blood through the obstructed orifice. Hypertrophy usually is accompanied by dilatation, which is as much a part of the adaptation as the hypertrophy, for in most of the conditions which are followed by hypertrophy the cardiac cavity involved must accommodate a greater amount of blood. The weight of the hypertrophied heart may be increased up to more than three times the normal.

**ENDOCARDIUM.** The endocardium is more subject to infection than the intima of any other vessel in the body. This, to a large extent, is due to irregularity of surface, and to the action of the valves, which by contact and friction of surfaces mechanically favor the access of infectious organisms. However much are the variations in the anatomical appearances of the lesions, and however much the causes vary, the mode of production of the lesions is the same. Anatomically two main types are recognized *endocarditis verrucosa* and *endocarditis ulcerosa*. In both, the process is essentially an infectious thrombosis. The most common lesions in the verrucose form consist in the formation of warty or papillary masses along the line of closure of the valves. They may be so small

and transparent as to be recognized with difficulty by the naked eye or may form large, irregular masses a centimeter or more in diameter. On section, the mass has the character of a blood plate thrombus with a varying admixture of fibrin and corpuscles. Bacteria, in enormous numbers and taking the form of colonies, often are found in the thrombi. At the point of attachment the endothelium is absent and there is a superficial necrosis of the valvular tissue with infiltration of leucocytes and proliferation of the cells at the edge of the necrotic tissue. In the more severe types of infection there may be extensive necrosis and no evidence of reaction on the part of the tissue. The leucocytes in the thrombus usually are broken down, forming masses of nuclear detritus. The milder degrees of this form of endocarditis are common and recovery can take place without the production of permanent functional injury, only a slight thickening of the valve resulting. When the thrombus formation is more extensive, organization takes place and the thrombus is replaced by granulation tissue which finally results in great cicatricial thickening of the valve and the production of an uneven often papillary surface. The formation of cicatricial tissue may extend for a distance, involving, in the case of the mitral valve, the chordæ tendineæ in the process. The valves may be shortened by the formation and contraction of the cicatricial tissue, they may grow together at their opposed edges, and by the contraction of the chordæ tendineæ, the edges of the mitral valve may be drawn down into the ventricle in the shape of a funnel. There frequently is a deposit of lime salts in the cicatricial tissue, changing the valve into a hard, unyielding mass. There is a great liability to recurrent attacks, due to the persistence of the infectious agents in the body and to the increased opportunity given for the lodgment of bacteria by the great irregularity of surface. In ulcerative endocarditis, the cause of which is most frequently the pyogenic bacteria, particularly the staphylococcus aureus, there is extensive softening and destruction not only of the thrombus but of the necrotic tissue of the valve. Valves may be perforated or entirely destroyed. Although acute endocarditis generally affects the valves, other parts of the endocardium may be affected primarily and the process may extend from the affected valves to the adjacent surfaces; particularly is this true in the ulcerative form, in which there may be extensive necrosis, abscess formation

and ulceration in the myocardium. These various forms of endocarditis, particularly the ulcerative, are a frequent source of emboli in the arterial system. Endocarditis is much more frequent in the left than in the right side of the heart and the mitral valve is somewhat more frequently attacked than is the aortic.

In consequence of the lesions produced the action of the valves is interfered with. By shortening and contraction they may no longer close the orifices, *insufficiency*, or by their induration and the union of adjoining edges they may narrow the orifices, *stenosis*. In most cases both stenosis and insufficiency result. Valvular aneurysms may result from partial destruction, the thin portion of the valve gradually dilating under the blood pressure.

**VEINS.** They are more frequently the seat of infections than are the arteries because of the greater slowness of the blood current, the relatively greater surface and the irregularities of surface due to the valves. Acute inflammation of the veins, *phlebitis*, is due to infection either from the blood stream or to extension of a neighboring infective process, and leads to the formation of thrombi. By *varicose veins* is understood dilatation of the lumen usually with elongation of the vessel and thickening of the walls. It is most frequent in the subcutaneous veins of the lower extremities, which appear as thick tortuous or worm-like cords beneath the skin. On section, the thickened wall is formed chiefly of cicatricial tissue and the lumen is irregular. Both occluding and mural thrombi are not uncommon and by their organization add to the amount of cicatricial tissue. The condition seems to be due to some congenital weakness or imperfection in formation of the wall, added to by increased venous pressure.

**ARTERIES.** The frequent and important pathological changes in arteries are due primarily to imperfections in structure. The structure is admirable for its functions. The combination of smooth muscle and elastic tissue in the large conducting arteries gives the necessary components of strength and elasticity, and the predominating muscular tissue in the small distributing arteries, under the control of the vaso motor nerves, provides for the necessary regulation of local blood supply. There is a degree of functional adaptation beyond this, for the artery can both enlarge by growth, as is seen in the increase in size of anastomosing branches after the closure of a main stem, or diminish in calibre, this taking place in

extreme cases by the formation of a new artery with perfect coats inside of the old. Newly formed blood vessels can undergo a differentiation into arteries and veins as in the embryo. There is a definite regulation between blood supply and blood demand, which regulation when it passes beyond the limits of the physiological contraction and expansion is effected by growth. It seems probable that such regulation is not perfect and that it carries with it a loss of the power of adaptation. The greatly enlarged hypertrophied heart has enlarged coronary arteries, but the frequent association of interstitial lesions with the hypertrophy shows a greater vulnerability of the tissue, which may be due, in part at least, to an imperfect adaptation of the blood supply to the greater needs imposed upon it. The imperfect character of the structure of the arterial wall is made manifest by its nondurability, which is not counterbalanced by its capacity for repair. Various tissues are, in a complex way, united in the arterial wall, and, in regeneration, a complex architectural structure is not perfectly reproduced. New and perfect arteries frequently are formed, but repaired arteries always are imperfect. The nutrition of the wall is not amply provided for; save in the ascending aorta there are no blood vessels in the media, the nutrition being effected through the intima and the comparatively few vessels of the adventitia. Of all the tissues of the body the arteries are the most prone to the degenerations associated with age. Perfectly normal arteries rarely are found in individuals over forty.

**ARTERIO-SCLEROSIS.** The most common pathological condition found in the arteries is arterio-sclerosis. It appears in many forms, affecting sometimes circumscribed areas only, at others the entire circumference of the vessels; it may be a general process affecting, to a greater or less extent, all the arteries of the body, or may be confined to a single arterial system. It plays a prominent part in most of the organic diseases, especially those occurring after the age of fifty and is the most prominent of the senile changes. It consists essentially of circumscribed or diffuse thickening of the intima associated with degeneration of both intima and media. The first change is degeneration, which is followed by dilatation of the vessel and new formation of tissue in the intima at the point of dilatation. The primary change is a fatty degeneration of the elastic and connective tissue of both intima and media. Such areas

appear as opaque, white or yellow streaks extending longitudinally. The degenerated elastic fibres not infrequently break and their edges curl up. The muscular tissue also shares in the degeneration and the cells become fatty and hyalin. The thickening of the intima appears later and may take the form of projecting plaques which seem to be laid on the surfac. These are composed of dense sclerotic fibrous tissue in which a great number of elastic fibres and a few muscle fibres are intermingled. The cells vary in number and examination shows a large amount of fat in both the cells and tissue. The tissue formation is densest on the inner side and below this is an area containing numbers of lymphoid and epithelioid cells, the latter usually being swollen and filled with fat lying in a homogeneous or hyalin tissue. Connective tissue formation in the media also follows the degeneration, but there is no elastic tissue formation. Sections of the small arteries show the same condition of degeneration and in some cases a complete disappearance of the media; uneven dilatation of the vessel and new formation of tissue in the intima is most marked at the site of the greatest dilatation. Rarely, even in the small arteries, do the changes uniformly affect equally the entire circumference. The fatty degeneration in the thickened plaques increases and softening takes place, resulting in the formation of an opaque white fluid in which cholestrin and fatty acid crystals may be found. Calcification in such areas is a common process, or the softening may continue and the area finally break through into the interior of the vessel producing an *atheromatous ulcer*. In the more strictly senile forms of arterio-sclerosis the process is more diffuse, the connective tissue thickening is less marked and the degeneration and calcification more evident. Calcification is more marked in the abdominal aorta and in the arteries of the lower extremities than elsewhere. It occurs first in plaques which finally involve the entire circumference, and, uniting, change the arteries into rigid calcareous tubes. Dilatation of the entire artery takes place with lengthening giving rise to tortuosities which are particularly evident in the splenic artery. Although the media normally is devoid of vessels, vessels are usually found in the degenerated tissue below the thickened media.

Much the same conditions as in the aorta may be produced in the cardiac valves resulting in thickening and contraction of the

tissue and calcification. This most frequently affects the aortic valves and the aortic leaflet of the mitral valve. The stenosis of the aortic valves due to the projection and frequent adhesion of the calcified leaflets may be extreme.

Syphilitic arterio-sclerosis. This is a special form of sclerosis which occurs chiefly in the ascending aorta and arch, but may be combined with the ordinary type of arterio-sclerosis. The essential lesions are in the media and consist in the formation of cellular granulation tissue with extensive necrosis and degeneration. In consequence of the necrosis the tissue is converted into a granular mass without nuclei and in which the wall lamination is still visible. Breaks and fractures of this tissue are common and into these rents the granulation tissue with its newly formed vessels extends. Giant cells often are found in the tissue and there may be definite gummata with surrounding necrosis. The intima is greatly thickened and presents a rough nodular surface often with definite cicatrices. The process may involve the entire circumference of the vessel or may appear in patches. The *treponema pallidum* is found in the lesions. The syphilitic process here is very similar to that of the endarteritis syphilitica of the small arteries particularly those of the brain and which often leads to complete closure of the lumen.

Periarteritis nodosa appears in the form of nodules on the small arteries; these show, on section, cellular infiltration of the wall with degeneration of elastic and muscular tissue.

In the course of acute infectious diseases a peculiar form of endarteritis often is seen, more frequently in the arteries of the pia mater and the spleen. This consists in a proliferation of the endothelial cells, often forming festoons projecting into the vessel and covered by flat endothelium. A similar condition is found less frequently in veins. It is uncertain whether or not this condition is associated with *endarteritis obliterans*, in which the calibre of the artery is narrowed by formation of connective tissue in the intima and which is not associated with degeneration of the media. The condition is to be distinguished from the compensatory narrowing of an artery which takes place when the vascular territory which it supplies is reduced. In endarteritis obliterans the connective tissue may appear at one point or affect the entire circumference. It is not at all unlikely that the condition often is due to the formation of



mural thrombi followed by complete organization. More rarely small foci of necrosis are found which begin in the intima and extend into the media. A small loss of substance results on which fibrin may be deposited and which later becomes covered with endothelium. The condition is not uncommonly found in the arteries of the submucosa of the intestine, in bacillary dysentery and in the arteries of the lymphoid follicles in typhoid fever. It is not impossible that such lesions may form the starting point of certain aneurysms.

**ANEURYSM.** This is a cavity communicating with the lumen of an artery and formed in whole or in part by dilatation of the wall. The formation of an aneurysm is due to degeneration of the arterial wall which becomes weakened at the area; the compensatory formation of connective tissue is not sufficient to withstand the blood pressure and dilatation takes place. Various forms of aneurysm are distinguished. An artery may be dilated over a large area, forming a *diffuse aneurysm*, or the dilatation may involve the entire circumference of the artery for a certain distance producing a *spindle-form aneurysm*. The most common and most typical is the *sacular aneurysm*, in which the dilatation occurs in a circumscribed area; the sac so formed is circumscribed and communicates with the lumen of the artery by an opening which usually is smaller than the cavity of the sac. Aneurysms may be single or multiple. In certain cases of arterio-sclerosis it is not uncommon to find numerous small sacs along the course of the artery (*cirroid aneurysm*).

Where the dilatation takes place there has been extensive degeneration of the arterial wall followed by connective tissue formation, so that the normal wall of the vessel is not represented in the wall of the aneurysm. Where the sac is given off from the artery the elastic tissue of the media passes for a variable distance into the aneurysmal wall. Sections made elsewhere may show fragments of elastic and muscular tissue, but the wall is composed principally of dense connective tissue, the fibres of which are fused and hyalin. The internal surface is irregular and covered in whole or in part by endothelium. Aneurysms almost invariably contain thrombi, which usually are deposited in layers. Sections of such thrombi show alternate layers of white and red thrombi. The most extensive thrombus formation is found in those aneurysms which connect

with the artery by a small lumen and in which there is the greatest opportunity for stagnation of the blood. The senile forms of arterio-sclerosis may be associated with diffuse dilatation of the vessels, but rarely lead to true aneurysms, and the same is true of general nonspecific arterio-sclerosis. Aneurysm is most common at an age prior to that in which arterio-sclerosis is most likely to occur. The frequency of aneurysm in the ascending portion and the arch of the aorta, those portions most affected by syphilitic arterio-sclerosis, together with the statistical evidence of the association of aneurysm of the aorta with syphilis points to this disease as an extremely frequent cause.

Aneurysms may form also when the degeneration of the wall is due to causes acting from without. When a tuberculous cavity in the lung comes in contact with a branch of the pulmonary artery and the tuberculous necrosis extends into the wall, an aneurysmal dilatation may take place at the weakened point and fill the entire cavity. The sudden and fatal hæmorrhages which take place in tuberculosis usually are due to the rupture of a small aneurysm of a pulmonary vessel. In the same way aneurysms of the aorta may be due to infections of the adventitia which extend into and weaken the media; and in rare cases they may be due to infections of the intima. Aneurysms may be formed also as the result of trauma. The tissue formed in repair is not so capable of resistance and gives way to the blood pressure.

A special form of aneurysm is known as *miliary aneurysm* and occurs more frequently in the arteries of the brain than elsewhere. They are multiple and like other aneurysms due to degeneration of the arterial wall, which, in the arteries within the brain tissue, is thin and slightly resistant. Hæmorrhage within the brain frequently is due to the rupture of such aneurysms. Another form of *aneurysm is the dissecting aneurysm*. This is due to an incomplete rent in the wall, and the blood current then forces its way into the tissue separating the coats. Such rents take place usually in arteries whose walls have been weakened by arterio-sclerotic processes. The blood may coagulate in the tissue, or in rarer case communication with the lumen of the vessel may be established by another fissure lower down. In this way a definite cavity which gradually becomes covered with endothelium may be formed around the artery and a double circulation be established. Such

dissecting aneurysms may also occur in arteries of small size. Pathological communication may be formed between veins and arteries either with or without the preceding formation of an aneurysmal sac.

An aneurysm when once formed continues to increase by expansion. All tissues gradually give way before the constant pressure and the hammering of the blood current. An aneurysm given off from the posterior portion of the aorta may produce erosion of the vertebræ where it comes in contact, and erosion of the sternum may be produced from aneurysm of the arch. The death of the individual with aneurysm frequently is due to rupture.

**EXPERIMENTS.** The experiments in circulation cover the simpler experiments in thrombosis and embolism and the physiology of certain pericardial, myocardial and endocardial lesions. (1) Under anæsthesia, aseptically expose the jugular vein of a cat, sear lightly with a hot platinum needle, and after three minutes, excise, fix, imbed and section. Platelet thrombosis occurs. (2) Under anæsthesia and aseptically, mechanically injure the jugular vein of a cat by pinching and twisting in a hæmostatic forceps. The carotid can be injured or tied off in the same animal and at autopsy twenty-four hours later, the thrombosis in both vessels studied. (3) Under anæsthesia, aseptically insert into the aorta of a dog, through the external iliac artery, by means of a special cannula a number of tobacco seeds. Manually compress the mesenteric arteries at the time of injection so as to avoid mesenteric infarction. Autopsy at the end of one week and study the infarcts in kidney and spleen, both grossly and histologically. (4) Inject 2 c.c. olive oil into the posterior auricular vein of a rabbit. Observe the symptoms, and after death perform autopsy, studying especially frozen sections of lung, brain, kidney stained with Scharlach R., for the oil (fat) emboli. (5) Under anæsthesia connect the carotid artery of a cat with the mercury manometer, make pneumograph connections and inject into the femoral vein 30 c.c. air in portions of 10 c.c. Study the tracings of blood pressure, pulse and respiration. Autopsy, clamping off the great vessels and open the heart under water to show the air in the right side. The auricle and ventricle frequently show foamy fibrin thrombi also. (6) Hydropericardium may be produced by opening the thorax of a dog under ether anæsthesia and artificial respiration, and injecting into the

pericardium from 30 to 75 c.c. olive oil. Connect the femoral artery with the manometer and note the depression of cardiac action shown in the kymographic tracings. (7) Aortic stenosis. Under ether anæsthesia and artificial respiration, open the thorax of a dog and constrict the aorta near its origin by means of a heavy silk ligature. Note the effects by the kymographic registration of heart action and blood pressure. (8) Aortic regurgitation may be produced in the same animal by introducing a valve hook through the carotid artery and tearing the aortic valve. The effect on the circulation is marked by a notable fall in pressure and the establishment of the water hammer pulse. All the valve lesions are to be studied with the multiple stethoscope. (9) Myocardial degeneration. Under ether anæsthesia and artificial respiration open the thorax of a dog and inject into the cardiac muscle, in numerous places, small amounts of 95 per cent alcohol. With kymographic registration note the great reserve force of the heart and the final fall in pressure and arrhythmia after a large part of the muscle has been incapacitated. (10) Arterio-sclerosis. Inject into the posterior auricular vein of a young rabbit three drops adrenalin. Inject daily for one week, increasing the dose by one drop each day. Autopsy at the end of two weeks and carefully observe the aorta, making sections of the vessel and of the cardiac muscle. The latter frequently shows myocardial degeneration, fibrous myocarditis and hypertrophy.





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## THE PATHOLOGICAL PHYSIOLOGY OF THE CIRCULATION

The amount of work accomplished by the heart is determined by the amount of blood it projects into the aorta in systole, the number of contractions in a given time, and the degree of arterial pressure which the blood overcomes in entering the aorta. The work even under normal conditions varies constantly and widely and the heart readily adapts its activities to meet new conditions. Increased demands for work are met by increase in the frequency and force of contractions. The various pathological conditions of the heart and pericardium affect the work by impeding the entry of blood into the heart, its passage through and from the heart and by diminishing its power of contraction.

Pathological conditions of the pericardium interfere with the function of the heart in two ways. (a) Accumulation of fluid within the cavity interferes with the entry of blood by increasing the pressure around the heart. The effect of the pressure is felt chiefly on the large vessels with relatively thin walls which enter the heart, and also on the auricles. The pressure on the venous side is increased and the blood pressure diminished by the small amount of blood which passes through the heart and into the aorta. Much depends upon the rapidity with which the fluid collects, for the cavity is distensible and the outer wall yields under pressure. In dropsical conditions in which the fluid collects very slowly very large amounts of fluid may exert but little pressure; on the other hand, a small amount of fluid rapidly formed, for example, an acute inflammatory exudate, produces very considerable pressure. The greatest degree of pressure will be produced in cases of rupture of the heart or of the great arteries within the pericardium, in which cases the pressure within the pericardium increases so rapidly that a small hæmorrhage prevents the expansion of the heart. But when the opening into the pericardial sac is small, very oblique or tortuous, the hæmorrhage, although constant, may be very slight and a large quantity of blood may collect before the pressure becomes sufficient to stop the heart. Tumors of the mediastinum

by the pressure which they exert on the heart or great vessels may act in much the same way as increased pericardial pressure. Pericardial pressure has a further interest in the fact that the circulatory disturbances produced cannot be compensated for by increased activity of the heart.

(b) Other pathological conditions of the pericardium can affect the work of the heart by interfering with its contraction. Simple obliteration of the pericardial cavity due to adhesions after pericarditis have little or no effect, but when, as is often seen in tuberculous pericarditis, the heart becomes surrounded by dense masses of tissue often 0.5 cm. thick, the presence of such an unyielding inert mass offers resistance to contraction. The condition becomes worse when thick pleuritic adhesions are added to the pericarditis. Under such conditions extreme hypertrophy and dilatation of the heart results.

The various pathological changes in the valves produced by endocarditis impede the passage of blood through and from the heart. The valves become incapable of closing the openings which they guard, *insufficiency*, through shortening brought about by destruction or contraction of cicatricial tissue, through adhesions to the cardiac wall and through contraction of the chordæ tendineæ. On the other hand, in *stenosis*, by adhesions between the valves and by calcification the openings may be diminished in size. In the majority of cases of valvular disease varying degrees of both stenosis and insufficiency are present. The normal muscular contraction of the heart is essential for the action of the auriculo-ventricular valves, for in the contraction the ring of insertion is diminished in size. Dilatation of the heart may produce a relative insufficiency of the valves by the enlargement of the orifices.

The simplest of these conditions is seen in the rare cases of uncomplicated stenosis of the aortic valves. This is overcome by hypertrophy of the left ventricle which enables it, by the increase in the force of contraction, to project the normal amount of blood in the same time through the narrowed orifice. Much more common is the condition in which the orifice is not only narrowed, but the valve incapable of accurate closure. The ventricle then must hold and project a much greater amount of blood, for a large proportion of the blood ejected regurgitates during diastole, from the aorta back into the ventricle. Not only this, but in diastole the ventricle is

more easily filled by the forceful backward flow from the aorta than from the auricle. A diastolic intraventricular pressure is produced which leads to increased pressure within the auricle and to hypertrophy. Stenosis of the mitral valve is a more complicated condition, for the increased pressure within the auricle extends into the pulmonary circulation and throws more work on the right side of the heart, for the blood must be forced through the lungs against pressure. Hypertrophy of the left auricle takes place, but no hypertrophy of the left ventricle because no increased work is thrown upon the latter. When, however, there also is insufficiency, the left ventricle dilates and hypertrophies as well, for in systole the normal amount of blood must be projected into the aorta in spite of the amount which regurgitates into the auricle. So important is the contraction of the heart in assisting the action of the mitral valve that an apparent insufficiency of the valve, as determined by autopsy, may not really have been such in life.

Valvular disease in the right side of the heart is much less frequent than in the left. In the rare cases of stenosis and insufficiency of the pulmonary valves the right ventricle hypertrophies. Hypertrophy of the right side of the heart, however, is more frequently the result of high pulmonary pressure brought about (a) by pathological conditions in the lungs which diminish the sectional area of the pulmonary vessels, or (b) by increase of auricular pressure on the left side of the heart. Hypertrophy of the right ventricle depending upon impediments in the pulmonary circulation from disease of the lungs varies in degree according to the disease. It is almost invariably present in emphysema of the lungs while in advanced destruction of lung tissue in cases of tuberculosis it usually does not take place. This is due to the fact that in tuberculosis the work of the heart is reduced by the invalid life of the patient, while in emphysema there may be but little impairment of the usual activity, and the work of the heart is increased not only by the diminution of the sectional area of the vessels, but in addition to this, the rapidity of the stream must be increased in order that the diminished respiratory surface shall suffice for oxygenation.

*Hypertrophy* of the heart takes place much more easily in the young than in older persons, and slight valvular defects in the young may be so perfectly compensated that an efficient circulation is maintained. In most cases the heart which has compensated for

an injury, however perfect the compensation may appear, is not as perfect a machine as the normal heart, in that there is diminished reserve force. The compensation demands increased resistance to dilatation under increased fluid pressure, as well as increased force of muscular contraction. The power of the dilated heart is weakened owing to the increase of the surface area over which the pressure must be raised. Conditions which increase the work of the heart, such as severe exercise, psychic disturbances, pregnancy, or those producing degrees of degeneration of the muscle fibres as infections and fever, which could easily be met by the reserve force of the heart, may quickly break down the compensation in both pressure, resistance and force contraction. The dilatation which then occurs adds to the valvular imperfections by the dilatation of the orifices. Probably in the hypertrophied heart there also is less in the power of resistance of the hypertrophied muscles fibres to pathological conditions acting upon them and also a loss in the reserve nutritive capacity of the coronary circulation. The diameter of the coronary arteries does not increase *pari passu* with the increased size of the heart and pathological conditions of the myocardium are much more common than in normal hearts.

All the pathological conditions of the myocardium act by interfering with both the resisting and contractile power of the heart. Apart from the acute degenerations of the muscle fibres due to the action of toxic substances engendered in the course of infections, the most serious lesions of the myocardium are in connection with disease of the coronary arteries. Complete obliteration of one coronary artery or even a considerable branch, if produced suddenly, is usually fatal. Closure of a smaller branch may be followed by necrosis and infarction of the area which it supplies. Chronic degeneration of the myocardium, followed by formation of connective tissue (fibrous myocarditis), frequently is associated with arterio-sclerotic changes of the vessels. Sudden death may result from narrowing of the calibre without occlusion. In such cases apparently, the blood supply may just suffice for the mean activity of the cardiac muscle and any sudden demand for increased blood supply cannot be met. The degeneration of the myocardium, involving the auriculo-ventricular bundle of His, brings about a disturbance of the associated contraction of auricle and ventricle. The action of the heart, whether the neurogenic or the myogenic

theory of contractility is accepted, is influenced by nervous supply, and disease of the nerves may affect it, producing abnormal frequency of contraction (tachycardia), or abnormal slowness (bradycardia), or various grades of arrhythmia.

When the heart, either temporarily or continuously, is *insufficient* that is, is incapable of doing the normal amount of work, there occurs a fall in the arterial pressure due to the diminished output of blood into the aorta and an accumulation of blood on the venous side producing increased venous pressure. All the disturbances which arise in consequence of insufficiency of the cardiac force lead to a slowing of the blood current, which is of more importance for the function of the organs than the diminution of the blood pressure. A diminution of the blood pressure primarily brought about by a diminution in the amount of blood projected by the systole into the aorta is compensated for by contraction of the small arteries which brings the diminished blood amount into a diminished vascular territory. The normal metabolism of the tissues depends not only upon the proper quality of the blood, but on the amount which, in a given time, passes through the vessels. The activity of the lymphatic circulation is closely dependent upon that of the blood and increase of venous pressure is followed by increase of pressure in the lymphatics. The slowness of the circulation in the lungs brings about the respiratory distress, the *cardiac dyspnoea*; the diminished oxydation of the blood gives a blue color to the skin and mucous membranes, *cyanosis*. With the continued cardiac weakness and the venous congestion, gravity operates more readily and, as a result, the blood accumulates and the circulation becomes least active in the most dependent parts. With the consequent diminution in metabolism the resisting power of the tissues is diminished and infections easily occur. The relation of infections to passive congestion is complicated. In passive congestion of the lungs the resistance of the tissue to infection with the tubercle bacillus is increased and an actual infection may take a more favorable course. The artificial production of passive congestion acting by filling the tissue with bactericidal fluids may favorably influence various local infections. Regeneration of tissue does not take place so readily, and the healing wounds and inflammatory conditions generally do not pursue a favorable course. Nutrition is impaired not only by the character of the circulation in the tissues

but also by the interference with digestion and absorption from the intestinal canal. A vicious circle is established in which a condition resulting from an imperfect function tends to increase the preceding functional imperfection. In all these cases there can be compensation brought about by diminishing the demands made upon the heart by bodily activity until life is possible only in bed and finally even so much activity as is involved in existence becomes impossible.

In chronic passive congestion two changes are almost invariably found in all tissues. There is diapedesis of red blood corpuscles from the dilated capillaries and increased formation of the interstitial tissue of organs, with associated formation of elastic tissue. It is uncertain whether such a growth of tissue is due primarily to the passive congestion or whether it is secondary to pathological conditions of the parenchyma. Passive congestion produces certain changes in the organs of the body more or less characteristic of each. Passive congestion may be brought about in organs also, by local obstruction to the venous outflow. Occlusion of single veins may produce little or no result, owing to the number of collaterals. Pathological conditions in the liver producing obstruction in the portal circulation lead to passive congestion in the entire portal territory.

**PASSIVE CONGESTION OF THE LUNGS.** In this the lungs do not collapse so completely on opening the chest, and are heavier, more moist and more resistant than normal. The color is dark red, which, in more chronic cases, passes into a brick red (brown induration). The greater consistency of the lung is due, in great part, to the greatly dilated capillaries which project as loops into the air spaces. The alveolar epithelium is, in part, desquamated. There is, not infrequently, fluid in the alveoli and also red corpuscles which pass in by diapedesis. These corpuscles, in part, pass away by the lymph streams, in part they are taken up by the phagocytic alveolar epithelium and converted into brown iron-containing hæmosiderin. Not infrequently the pigment forms around small particles of carbon which the cells also have taken up. The consistency of the tissue also is added to by an increase in the interstitial tissue.

**PASSIVE CONGESTION OF THE LIVER.** In recent cases the liver is enlarged, the capsule tense, the whole surface and section of the organ a dark red in which the central veins stand out as dark points.

When the congestion has lasted longer the dark areas around the central veins increase in extent and contrast sharply with a pale fat-containing periphery. This mottling of dark and light areas has given rise to the term "nutmeg liver," the appearance somewhat resembling that seen in the smooth section of a nutmeg. On microscopical examination there are three distinct conditions. In the first there is marked dilatation of the central veins and dilatation of the capillaries around these, extending a varying distance towards the periphery of the lobule. The liver cells in the area of dilatation are preserved but atrophied. In the second, in which the nutmeg appearance is very marked, the liver cells about the centres of the lobules have almost or completely disappeared, leaving areas which are converted into blood lakes. In this tissue the remains of capillaries can be found and, occasionally, atrophied and necrotic liver cells. In the third, there is a true hæmorrhage into the tissue, the blood being both in the capillaries between the cells and in the intervening parenchyma. In certain cases the capillaries seem to be collapsed and the slow circulation takes place chiefly through the intercapillary areas. In such a condition it is not improbable that there may have been a central necrosis of the liver in association with passive congestion. The necrosis in cases of endocarditis may have been produced at the time and the regeneration of the liver tissue has been inhibited by the imperfect circulation. It is also not improbable that the liver cells may have become necrotic, owing to imperfect nutrition. In the most advanced form, cardiac cirrhosis, there is a considerable formation of connective tissue in the centres of the lobules, associated with the atrophy. In these cases also there may be very marked formation of elastic tissue. There is little or no formation of blood pigment.

**PASSIVE CONGESTION OF THE SPLEEN.** The spleen is enlarged, of firm consistency, and, on section, of a dark red color. Microscopically, some hæmosiderin pigment usually is present in large phagocytic cells and in the fibrous trabeculæ; the walls of the veins and the reticulum of the pulp are thickened. A greater degree of congestion usually is present when the obstruction is in the portal vein than when it is due to cardiac disease.

**PASSIVE CONGESTION OF THE KIDNEYS.** These are large, firm and dark red. The congestion is more marked in the pyramids

which are sharply separated by color from the cortex, the venæ rectæ standing out as dark red lines. In the cortex the glomeruli are visible as red points. When the congestion is long continued there is a general increase of the fibrous tissue, more marked around the vessels and foci of glomeruli and tubular atrophy. Not infrequently small hæmorrhages are found between the tubules, and red corpuscles find their way into the lumina. Hyalin casts in small numbers always are present and on boiling the kidney or fixing thin sections in coagulating fluids, a granular albuminous precipitate often is found in the capsular spaces.

**PASSIVE CONGESTION OF THE BRAIN.** The changes are less evident than in other organs. The vessels of the meninges are prominent, there is some thickening, the tissue contains an excess of fluid and the pia arachnoid is more easily stripped from the convolutions than in the normal. The brain is somewhat redder than normal and the vessels of the white matter are more prominent on section. There is no increase of the neuroglia.

**PASSIVE CONGESTION OF THE INTESTINES.** The vast vascular area of the portal system is the reservoir in which the blood in venous obstruction chiefly collects. The mucous membrane of the intestines is thickened and dark red. The surface pile formed by the villi is more prominent. When the obstruction is central and the lymphatic pressure is increased due to the increased pressure in the superior cava, not infrequently the intestinal lymphatics are dilated and small white areas filled with chyle and representing varicosities are found in the mucous membrane. Although the hæmorrhage by diapedesis is considerable, there is no pigment formation in the tissue, the red corpuscles being quickly carried into the lymphatics and into the mesenteric lymph nodes which in extreme cases of congestion may be reddened by the blood in the sinuses.

The effect of arterio-sclerosis on the circulation is one of the most perplexing questions in pathology. From a purely physical aspect the arterial tubes may be irregular, dilated and lengthened, rendering their course more tortuous, and to a varying degree the inner surface is less smooth than normal. In certain cases, these purely physical alterations, of which the aneurysm is the most marked type, appear alone or are the most prominent, and they appear to produce little effect. The opposition to the current is easily overcome by a slight increase in the cardiac work without hypertrophy.



When the arterial disease is more general and the small arteries of the organs are diseased and converted into rigid conducting tubes, the influence of the vaso-motor nerves removed or diminished by the greater or less destruction of the media, the effect on the circulation is more serious. For one thing there is interference with the normal distribution of blood, and the reciprocal relation of vascular territories. Nor can there be maintained the perfect relation between blood supply and function. It is in these cases that high arterial pressure and heart hypertrophy are found. When the arterial disease is most marked in the arteries controlled by the splanchnic nerves, inhibiting the influence of these vessels in regulating the circulation, the effect on the circulation is most marked. A difficulty is found in separating from the influence of arterial disease, the influence of the almost constant accompaniment of disease of the kidneys. Independently of arterio-sclerosis chronic renal disease, producing destruction of tissue and loss of function leads to the presence in the blood of substances producing increase in blood pressure; the increased blood pressure in the arteries, already less resistant, increases the arterio-sclerosis; heart hypertrophy of the left ventricle results owing to increased work thrown upon it to overcome the arterial pressure; not infrequently the same sclerotic changes of the arteries affect the aortic and mitral valves interfering with their function; to the heart hypertrophy, dilatation is added, the disease of the coronary vessels producing lesions of the myocardium which renders the walls less resistant; the auriculo-ventricular valves first on the left, then on the right side become relatively insufficient and general passive congestion follows, with the evils attendant upon it. There is a vicious circle widening with ever increasing rapidity.

HÆMORRHAGE is the passage of blood from the vessels. Hæmorrhages into the tissues have received various names, as *petechiæ* for fine punctiform hæmorrhages, *ecchymoses* for larger macular areas of hæmorrhage, and *hæmatoma* when the mass of blood in the tissue has a tumor-like form. Hæmorrhage by *rhæxis* takes place when there is an evident rupture in the vessel; by diapedesis when no rupture is apparent. Rupture in vessels may result from wounds, from over distension, or from destructive processes, such as ulcers or necrosis, extending from without into the vessel. Hæmorrhage by *diapedesis* takes place from the capillaries and small veins and is

found in a great number of pathological conditions. In practically every form of inflammation some red corpuscles are found in the exudate. In many cases it is by no means certain that the corpuscles pass through an intact wall; in extreme dilatation of capillaries and small veins small fissures may be formed by the separation of cells. The small punctiform hæmorrhages of the serous surfaces, particularly of the epicardium, which so frequently are found in death from infectious diseases, have been attributed to the action of a toxin, producing necrosis, or to solution of the endothelial cells. Necrosis of tissue usually is associated with hæmorrhage, the corpuscles seeming to pass with great ease through the walls of the capillaries of the necrotic territory, as is seen in the infarction. Any congestion of the blood in a capillary territory usually is accompanied by diapedesis of red corpuscles; this is one of the most common conditions in chronic passive congestion.

In certain general and ill-understood conditions, as in scurvy and in purpura, these small hæmorrhages in the tissue form a prominent feature of the disease. The hæmorrhages which so frequently accompany jaundice are due probably to the toxic action of the bile salts on the endothelial cells. Recently the hæmorrhagic diseases have been the subject of intensive experimental and clinical investigation and, as a result, it seems clear that the clotting power of the blood is greatly diminished in their course. The clotting power depends on (a) the balance between prothrombin and antithrombin; (b) a sufficient amount of calcium salts, and (c) a sufficient amount of fibrinogen. Excesses of antithrombin, insufficient prothrombin and insufficient amounts of fibrinogen have been demonstrated in several human cases and in animals, the subjects of experimentally produced hæmorrhagic diseases. Such defects appear to have an important bearing on these diseases. Variations in the organized constituents of the blood also may be important since it has been found that a reduction in the number of platelets frequently accompanies hæmorrhagic disease. The relation of such reduction to these diseases has not definitely been determined.

CEDEMA is an increase in the amount of tissue fluid. When this affects the entire subcutaneous tissue the condition is described as *anasarca*, milder degrees are known as *dropsy* and when the fluid accumulates in the serous cavities, various names, such as *ascites* (belly), *hydropericardium*, *hydrothorax*, designate the cavity in

question. The formation of the tissue fluid, under normal conditions, is due to the intracapillary pressure tending to filter the plasma through the capillary walls; diffusion depending upon the inequality in chemical composition between the blood plasma and the fluid outside the capillaries; osmotic pressure which varies with the molecular concentration; secretion by the endothelial cells. The variations in the character and the amount of fluid in different parts of the body have led to the assumption that in different organs there is a variation in the permeability of the walls of the capillaries.

Oedematous tissues are paler than normal, owing to the relative diminution in the amount of blood; they are more transparent; on pressure the fluid can be forced out leaving a pit or depression and, on section, fluid exudes from the cut surface.

Oedema from obstruction. With no increase in the formation of the tissue fluid oedema may result from obstruction to the outflow. The number of lymphatic vessels is so great and the anastomoses so abundant that closure of single vessels has little or no effect. Even the thoracic duct may be occluded without the production of oedema. The most marked instance is the chronic oedema of the legs and scrotum due to extensive obstruction of lymphatics by *Filaria Bancrofti*. Oedema from the decrease of tissue pressure, as by removal of atmospheric pressure from a part, is closely related to obstructive oedema, although in this case to the effect of obstruction must be added increase in formation due to passive congestion.

Oedema from passive congestion; cardiac oedema. The oedema here is due to the increased venous pressure assisting in capillary filtration, on the principal that increase in pressure of the filtering fluid increases the rapidity of filtration; to increased permeability of the capillary walls due to their distention and malnutrition; probably there is also increase in osmotic pressure due to the retention in the tissue of products of cell activity. The oedema appears only when the passive congestion has been of long duration and varies with the duration and the intensity of congestion. The oedema appears first in the most dependent parts, in which the effect of gravity increases the congestion. Oedema also appears when the venous obstruction affects certain areas only as in obstruction to the portal circulation produced in cirrhosis of liver, ascites being the most common result.

**RENAL ŒDEMA.** Œdema is one of the most common conditions in renal disease. It does not coincide in presence or degree with the destruction of the kidney parenchyma. It is especially common in those forms of renal disease in which lesions of the glomeruli are most evident. Various theories have been advanced in explanation of such œdema, of which the most prominent are (1) the retention of substances in the tissue which increase the osmotic pressure of the tissue fluid, (2) the presence of substances in the blood which increase the permeability of the wall of the vessel.

#### A CASE OF CHRONIC AND ACUTE ENDOCARDITIS WITH STREPTOCOCCUS INFECTION

**Anatomical Diagnosis.** Chronic endocarditis of mitral and aortic valves; Acute endocarditis of mitral, aortic and tricuspid valves; Hypertrophy and dilatation of heart; General chronic passive congestion; General anasarca; Ascites; Hydropericardium; Hydrothorax; Infarction of lung; Streptococcus septicæmia; Focal necrosis of liver.

Female, white, age five years. Body well developed and well nourished. General anasarca. Face cyanotic.

**Peritoneum smooth.** The cavity contains 1800 c.c. of clear, straw-colored fluid. Mesenteric lymph nodes normal. Diaphragm on left side at seventh rib, on right side at sixth intercostal space. Each pleural cavity contains a large amount of fluid similar to that in the peritoneum.

**Pericardial cavity** contains 300 c.c. of similar fluid. The heart weighs 450 grams. All cavities distended and filled with fresh clot, the heart appearing enormously enlarged. On the tricuspid valve are fibrinous and translucent elevations not over 1 mm. in diameter, scattered closely along the line of junction of the valve curtains. The columnæ carnæ of the ventricle are prominent. The wall is 6 mm. thick. The pulmonary valves are normal. The left auricle is much dilated and hypertrophied. The mitral valve presents a funnel-shaped opening, the edges of the valves irregular, greatly thickened and shortened. This condition extends to the chordæ tendinæ. The aortic valves are thickened and shortened. Along the free edge of both mitral and aortic valves are numerous minute vegetations, the edges not over 2 mm. in diameter, appearing as irregular translucent or pink excrescences along the irregular edges of the valves. The wall of the left ventricle is 12 mm. thick.

**Lungs.** Pleural surface smooth, on section the consistency greatly increased, the tissue of a brick red or brown color. There are three

areas, two in the right and one in the left lung, wedge-shaped, with the base on pleura, dark red in color, sharply circumscribed, a solid edge projecting both from the cut surface on section and above the pleural surface. The largest of these areas is 3 cm. in diameter.

Spleen weighs 125 grams. Deeply congested. Consistency increased, pulp dark red, trabeculae prominent, malpighian bodies not visible.

Liver, weight 1200 grams. Consistency increased, on section typical nutmeg marking appearing as small, irregular brown or red areas in a field of yellow.

Gastro-intestinal tract shows injection of the mucous surface.

Pancreas normal.

Kidneys firm. On section pyramids deep red brown in color, cortex paler. Markings distinct. Glomeruli appear as red pin point specks. Pelvic organs normal, aorta normal. Organs of the head not examined.

Microscopical examination. Sections of the mitral valve show great sclerotic thickening of the valve with polynuclear leucocytes and lymphocytes around the small vessels in the valve. The nodular projections on the free edge are composed chiefly of masses of blood plates with some fibrin and red blood corpuscles. Immediately beneath this and in the substance of the valve are large masses of polynuclear leucocytes and red blood corpuscles, among which are a few cocci in chains and not enclosed in cells. Section of the liver show the capillaries about central vein much distended and the liver cells atrophied. This is sometimes symmetrically concentric about the central vein, but is often irregular. The liver cells in the centre of the lobules contain considerable golden yellow pigment. Small areas of necrosis are irregularly distributed in the lobule, the necrotic cells being invaded by polynuclear leucocytes. The blood cultures made at autopsy gave the streptococcus pyogenes in pure culture.

REMARKS. The condition dates from the primary infection of the mitral valves, the date of which cannot be ascertained. There was, at this time, destruction of tissue of both valves of the left heart, but particularly the mitral, which, with the thickening and contraction, rendered them insufficient. There does not seem to have been stenosis. The heart hypertrophy, general passive congestion, anasarca and dropsy followed. The vegetations on the valves are due to a fresh infection of the valve surface by the streptococcus. This organism was found not only in the valvular lesion, but in the cultures made from the blood. The infarction of the lung is due to emboli from the fresh vegetations on the tricuspid valve. The liver shows the well-marked lesions of chronic passive

congestion and in addition focal necrosis. Focal necrosis of the liver is very frequently associated with streptococcus infection. The necroses are usually much more symmetrically placed around the central vein, but they may be irregular, as in this case. The liver necrosis is due to the action of toxins.

#### A CASE OF CHRONIC AND ACUTE ENDOCARDITIS WITH INFARCTIONS

**Anatomical Diagnosis.** Chronic mitral endocarditis; Acute vegetative mitral tricuspid and pulmonary endocarditis, with perforation of mitral valve; Hypertrophy and dilatation of heart; Eccymoses of epicardium; Œdema of pia; Old hemorrhage and cyst of softening in right internal capsule; Chronic passive congestion of lungs, liver, spleen and kidneys; Infarction of lungs, spleen and kidney; Chronic fibrous pleuritis; Chronic perihepatitis; Chronic perisplenitis; Anasarca (hydrocele, hydrothorax, ascites); Congestion and œdema of pharynx and larynx; Streptococcus septicæmia; arterio-sclerosis.

White, male, age twenty-four years. Body well developed and well nourished. Chest symmetrical. Marked bulging of precordial region. Rigor mortis present. Lividity of face and dependent parts. General œdema, most marked in scrotum and in legs.

**Peritoneal cavity.** Contains 100 c.c. of blood-stained fluid. Peritoneum lusterless. Splenic flexure of colon, firmly adherent to hilum of spleen by old fibrous bands. Appendix 6 cm., free, directed inward and downward. Mesentery lymph nodes slightly enlarged. Diaphragm at fifth intercostal space on left side, at sixth space on right side. Bladder markedly distended.

**Pleural cavities.** Left side contains 500 c.c., right 1000 c.c. of dark red fluid. Few old fibrous adhesions over both apices. Inferior surface of lower right lobe firmly bound to diaphragm by old fibrous bands.

**Pericardial cavity.** Contains about 300 c.c. of clear, straw-colored fluid.

**Heart.** Weight, 560 grams. Heart is about double the normal size and distended with clotted blood. The coronary veins are dilated. In the epicardium are innumerable ecchymoses discretely sown. On opening the heart, the mitral valve is found to be contracted, thickened and calcareous, so that the opening measures only 4 cm. in circumference. The free edge of the valve curtain is, moreover, studded with minute wart-like, soft vegetations, projecting 2 to 3 mm. from the edge of the valve. Between the base and free edge of the valve is an aperture 0.5

cm. in diameter, the edge studded with minute vegetations. The chordæ tendineæ are considerably thickened and shortened. The aortic valve appears normal save for a single vegetation 0.2 cm. in diameter upon the corpus aurantium of the middle cusp. The left auricle is greatly dilated, the wall hypertrophied. The left ventricle is 1.25 cm. in thickness. The muscle is firm and dark red. The right side of the heart is much hypertrophied; the right ventricle measuring from 0.75 to 1.25 cm. in thickness. The muscle is firm and shows on section light-colored areas. These light-colored areas are also seen on the endocardium lining the right ventricle.

The tricuspid valve opening is enlarged, 13 cm. in circumference. The free edge of the valve curtain shows discrete and confluent wart-like vegetations similar to those described on the mitral valve, projecting 2 to 4 mm. from the edge of the valve. Their transverse diameter averages 3 mm. The pulmonary valve is normal, save for one minute vegetation, 2 by 2 by 2 mm., situated directly between two of the cusps, a little back from the free edge of the valve. The coronary arteries are normal.

Lungs. Voluminous, heavy, firm and resistant, and of dark reddish brown color, with darker and firmer areas over the anterior surface of lower lobes. Upper lobes crepitate and pit on pressure. Cut section; anterior surface, upper left, shows a well-defined dark red, firm, elevated, dry, wedge-shaped area, with base toward surface 6 by 3.5 by 9 cm. On anterior surface, right lower lobe, are two similar areas 2 by 1.5 by 2.5 cm. and 1.5 by 1.5 by 2 cm. The surrounding tissue on pressure emits dark frothy fluid. Pulmonary artery and its larger distributing branches show discrete yellowish areas of thickening. Cruor clot in pulmonary veins. No thrombus or embolus detected.

Spleen. Weight, 140 grams. Very firm. Capsule thickened over superior surface and in region of hilum. Old fibrous adhesions attach it to diaphragm and splenic flexure of colon. A dark brown red area 1.5 cm. in diameter on anterior surface of same consistency as splenic substance. On superior border, yellowish-white, wedge-shaped area 1.5 by 0.75 cm. Malpighian bodies seen as small translucent dots very thickly sown. Trabeculæ quite prominent. Pulp does not readily come away on scraping.

Liver. Weight, 1920 grams. Large, firm, deep red organ, edges rounded. Anterior surface, right lobe, attached to diaphragm by long fibrous cords. Tip of left lobe firmly bound down to diaphragm by thick fibrous band. On section fairly resistant mottled red and yellowish white stellate areas (nutmeg appearance). Central vessels engorged, peripheral vessels collapsed.

**Kidneys.** Weight, 340 grams. Right organ much smaller than left. Capsule thickened and strips with difficulty, bringing away cortical substance. Surface pale red, lobulated and granular. On section cuts with difficulty. Cortex thinned irregularly, and showing faint red parallel lines running to surface. Glomeruli visible as fine sand-like particles. Pyramids dark red and markedly striated. Right kidney shows several grayish white, fine, dry, wedge-shaped areas with the base on the surface. The left kidney is firm, swollen and congested.

Adrenals normal.

Gastro-intestinal tract apparently normal.

Pancreas normal.

Bladder normal.

Genital organs normal.

**Aorta.** Diffuse yellowish areas of thickening, in places calcified.

**Organs of neck.** Tissue about pharynx, larynx and trachea show congestion and œdema.

**Head.** Brain, weight, 1490 grams. The vessels of pia injected. The membrane moist, stripped easily from convolutions. Ventricles contain about 5 c.c. of clear, yellowish fluid. On the floor of right lateral ventricle extending from the anterior edge of the eminence formed by the caudate nucleus to the posterior edge of the eminence of the optic thalamus, and external to both, is a yellowish elevated area 3.5 cm. long by 0.75 cm. in width. In the substance of the right hemisphere beneath elevated area described, extending antero-posteriorly between the caudate and lenticular nuclei is a cyst flattened horizontally, 4 cm. long, 1 cm. wide and 0.5 cm. high. This cyst is divided transversely into four chambers by thin fibrous partitions, and filled with soft, brownish debris containing bright yellow masses.

Middle ears normal.

Cultures from blood and organs gave streptococci.

**REMARKS.** A case of much interest in the interrelation of lesions. The pathological condition began with an acute endocarditis of the mitral valve. The primary disease may have been of a severe character or, as often happens, there may have been a number of attacks, the result being thickening, adhesion and contraction of the valve producing mitral stenosis and the changes of the heart dependent upon this. In the terminal acute attack the valves of the right side of the heart were also affected and there was further extension of the disease of the mitral valve producing a perforating ulcer of the valve. In consequence of dilatation of the right ventricle, the tricuspid valve became rela-



tively insufficient producing the marked passive congestion and cardiac oedema. Notice that the oedema is most marked over the lower extremities and scrotum, and in the serous cavities the accumulated fluid has a red tinge due to admixture of blood. The chronic passive congestion in the lungs is marked and has produced oedema and hæmorrhage into the alveoli. There are a number of fresh infarctions due to emboli from the vegetations on the cardiac valves. The cyst in the brain is the result of embolus and infarction. In this there is necrosis and hæmorrhage, which may have been greater in amount than is represented by the size of the cyst. The clot contracts and the serum is absorbed. Section of the area would have shown at this stage a slight amount of fibrin and numbers of large phagocytic cells containing blood pigment and fat from the necrotic brain tissue. The cyst is surrounded by neuroglia. The area does not undergo organization and contraction, as it does in other tissues, for connective tissue forms to but a slight extent in the brain and cicatricial contraction does not take place owing to the closed cavity of the skull.

Of further interest in the case is the arterio-sclerosis of the aorta and pulmonary artery, in consideration of the age. The pulmonary arteries are but rarely affected in arterio-sclerosis and in this case the condition is probably related to injury of the arterial wall by the increased blood pressure. Arterio-sclerosis of the aorta to the extent described here is not very uncommon at this age. Notice that the kidneys are unequally affected; the left, save for the passive congestion, is normal while the right contains recent infarcts and in addition is irregularly atrophied and contracted, a condition probably due to infarctions which were formed at the time of the primary attack.

#### A CASE OF EXTREME DILATATION OF THE HEART WITH CHRONIC MITRAL STENOSIS AND EMPHYSEMA OF LUNGS

**Anatomical Diagnoses.** Old endocarditis of the mitral valve with stenosis and insufficiency; Chronic emphysema of the lungs; Heart hypertrophy and dilatation; Subacute and chronic glomerular nephropathy; Chronic perisplenitis and perihepatitis; Passive congestion of the liver with cirrhosis; Chronic pancreatitis; General passive congestion; Ascites; Hydrothorax and hydropericardium; General anasarca.

White, male, 67½ years of age; occupation, butcher. First seen in January, 1899, when his symptoms were dyspnoea and feeling of exhaustion after exertion. From this time until 1901 he was more or less of an invalid. All symptoms pointed to faulty myocardial compensation. During the spring and summer of 1901 was very sick. At this time, on examination, the cardiac area much increased. The hepatic pulsation was marked; there was pulmonary oedema, ascites, oedema of extremities and to some extent of the body. All dimensions of the heart were increased, the apex beat was diffuse and four inches outside of the nipple line. Action of heart irregular and tumultuous, the entire thorax being shaken by the pulsations. The liver dullness extended a hand's breadth below the costal cartilage. The urine contained blood and a large amount of albumin with granular and hyalin casts. On March 31st, 1908, seen again. The dyspnoea on exertion was more marked. Heart area appeared more than twice the normal size. Heart sound loud and heard distinctly in left axilla. There is a mitral murmur. Heart apex 2½ inches below and 1½ inches to left of nipple line. Hepatic area greatly increased, nearly on level with umbilicus. Marked pulsation over liver and whole chest. No evidence of fluid in abdominal cavity. Urine showed large amount of albumen, hyalin and granular casts. Weight, 195 pounds.

In June, 1909, weight about the same. There was general oedema and the cardiac symptoms were exaggerated. Urine rather scanty. On October 5th, phlebitis and thrombosis of left leg, which was relieved by elevation of leg and bandage. On January 8th, 1910, four quarts of blood-tinged fluid were removed from abdominal cavity. During January and February he was tapped four times. All symptoms became exaggerated and he spent most of the time in bed. Died suddenly, March 5th, 1910.

The body, 5 feet, 10 inches long, weight 195 pounds. Body heat still present, no rigor mortis (autopsy 5 hours after death). The face dusky purple. There is a general oedema of the body most marked in lower extremities and in scrotum which measures 40 c.c. in circumference. There is desquamation of epithelium over ankles and legs. Moderate post mortem lividity. The abdomen distended rising 8 cm. above level of sternum. Subcutaneous fat in moderate amount, the tissue oedematous.

The peritoneal cavity contains (estimated) about 4000 c.c. of clear, slightly reddish fluid. The lower border of the liver in middle is 9 cm. below the sternum, and in the nipple line 6 cm. below the rib border. The peritoneal surface injected and cloudy. Dense adhesions about spleen and liver. There is a large amount of fat in the mesentery. All

the veins, particularly those in the lesser omentum, are greatly dilated. The mesenteric lymph nodes are somewhat enlarged and oedematous. A series of lymph nodes adjoining the splenic vein and the post peritoneal lymph nodes are enlarged and of a brilliant red color. The diaphragm at the lower border of the fifth rib on right side, at the sixth rib on left. The lungs free from adhesions. In each pleural cavity a considerable amount of clear, straw-colored fluid.

The pericardium fills the entire space between rib margins, only about 6 cm. of the upper portions of lungs visible. In the pericardial cavity a large amount of clear, slightly yellowish fluid. No adhesions.

The heart enormously enlarged, surface smooth. Epicardial fat in fair amount. The heart measures with cavities distended 21 cm. in length, 16 cm. wide and 8 cm. antero-posteriorly. The great increase in size principally on right side. Weight of heart, 780 grams. The circumference of right auricle 5 cm. above the tricuspid valve is 27 cm. The circumference of tricuspid valve at attachment is 17 cm., length of right ventricle 17 cm. The distension of the auricle is so great that spaces 1 cm. wide appear between the muscoli pectinati, the auricle resembling a distended bladder. The myocardium is normal in color, no evidence of fibrous myocarditis. The average thickness of wall of right ventricle is 4 mm. The left auricle is enlarged, the endocardium thickened and opaque, circumference of auricle 18 cm. The left ventricle is hypertrophied and somewhat dilated. The mitral valve, particularly the aortic segment, is contracted and in part calcified. The chordæ tendineæ are thickened and shortened. The edges of the valves adherent. The circumference of mitral opening 5.5 cm. Both coronary arteries soft and free from clots. The right greatly dilated, the circumference before branching 1.4 cm. The left slightly dilated.

Arteries. The arteries throughout the body generally in good condition. No calcification in large or medium arteries. In the aorta, particularly in thoracic and abdominal portions, a number of elevated plaques some of which show slight calcification.

Lungs. Pale, air containing throughout, no oedema. Mucous membrane of bronchi pale.

Spleen, weight 330 grams. Capsule thickened, areas of pale, dense cartilaginous-like tissue in capsule. On section consistency increased, coarsely trabeculated, hyperæmic, follicles not visible, splenic vein greatly dilated.

The liver enlarged, weight 2050 grams. Numerous adhesions, capsule thickened, surface finely irregular with here and there deeper depressions. Along the anterior border of the liver there is a fine granulation

of the surface, the granules distinct giving the appearance of grains of fine sand. Color, dark brown with paler foci. On section, consistency increased, the lobulation indistinct, with alternating dark and pale areas. The vena cava at liver greatly dilated, its walls thickened, circumference 11 cm. The hepatic veins all dilated, their walls thickened. The portal vein somewhat dilated. Gall bladder small, the ducts free.

Gastro-intestinal tract. The veins of the œsophageal plexus distended. The mucous membrane of stomach and intestines is injected. Otherwise normal.

Adrenal glands normal.

Pancreas. Firm, consistency increased. In pancreatic fat there are numerous small calcified foci.

The kidneys weigh 340 grams. Of the same size and general appearance. On the surface of the right kidney several deep cicatrices. The capsules somewhat adherent. The cortex rather pale, markings obscure. Pyramids deeply injected. The pelvic fat increased in amount.

Genitalia and bladder normal.

Microscopical Examination. Kidneys show focal and slight diffuse increase in the connective tissue of cortex. The convoluted tubules are somewhat dilated, the epithelium small. In the capsular spaces of glomeruli, which are distended, there is granular coagulum. The walls of the capillaries of the glomeruli are universally thickened, in places the lumina are closed by endothelial cells, polynuclear cells and cellular detritus. The capsular epithelium of the tufts is swollen and the cells increased in number. In several places the glomerulus opposite the entering vessels has become attached to the capsule with vascular connection between the capsular and the glomerular vessels. In the larger arteries of the kidney there is well-marked arterio-sclerosis, but is not evident in the glomerular arteries. The blood vessels are generally injected, particularly those of the pyramids. No distinct points of hemorrhage are found. The glomeruli contain a small amount of blood. A few red corpuscles are found in the tubules.

The pancreas shows a very considerable formation of connective tissue about the ducts forming a definite network extending throughout the organ. In addition there is a diffuse formation of connective tissue with atrophy of the parenchyma extending into the acini. All the Islands of Langerhans are well preserved. The bloodvessels are injected. The arteries show slight degrees of arterio-sclerosis.

In the lymph nodes adjoining the mesentery the sinuses are distended with blood. The lymphoid tissue is normal. All the blood vessels of

the node are strongly injected. The afferent lymphatics are greatly dilated and contain granular detritus and blood.

Sections of the lung show great dilatation of all of the pulmonary veins with a high degree of sclerosis of their walls. The lung is emphysematous. The alveolar walls in places are slightly thickened and congested. The alveoli are free from exudation, but contain a few large cells containing blood pigment.

The section of myocardium of the right ventricle shows well-marked congestion and general increase in the connective tissue and œdema. All of the fibres are, to a great extent, separated from one another. Some of the fibres are considerably enlarged, but they are in general well preserved.

**REMARKS.** The case presents many features of interest. The history is that of a chronic disease of the heart with valvular incompetence. The condition probably began with an acute endocarditis of the mitral valve, producing a stenosis and insufficiency, which was followed by hypertrophy of the right heart and dilatation. The work thrown on the right heart was greatly added to by the chronic emphysema of the lungs. The man was a butcher by occupation, this entailing hard work at intervals. It is not impossible that there was a considerable degree of dilatation of the heart in the beginning, associated with the mitral endocarditis and that it increased gradually to the enormous degree described. The dilatation of the right heart is extreme and the tricuspid valve was functionless. The hypertrophy, though considerable as shown by the weight, is inconspicuous compared with the dilatation. There was also some degree of chronic nephropathy which by the increase in blood pressure incident to this added to the cardiac work and this was materially added to by the subacute glomerular nephropathy, which probably dates from an acute erysipelas which he is said to have had in the summer preceding death. The cicatrices noted in one kidney can be traced to infarctions due to emboli from the mitral valve.

The impediment to the passage of blood through the heart led to chronic congestion in the systemic veins. The condition in the liver shows atrophy, destruction of tissue and following this an increase in the connective tissue in both areas in the lobule. The systemic veins in all the organs show the same condition of passive congestion. The general œdema and collection of fluid in the

thoracic pericardial and peritoneal cavities are referable to the chronic congestion and to the associated nephropathy.

The condition in the lymph nodes is an interesting one. Red lymph nodes, known as hæmo-lymph nodes, have been described in post peritoneal tissue of various animals, including man, and the presence of red marrow tissue has been described in the sinuses. In the condition here the blood in the sinuses has been brought by the afferent lymphatics from small hæmorrhages in the tissues resulting from the passive congestion.

In chronic thickening of the capsule of the spleen the formation of the hard masses described is not uncommon in some cases extending over the entire surface, in others, as in this case, in foci. They are formed of dense, sclerotic tissue arranged in laminæ and containing few cells.

It is usual to have in such cases clinical evidence of œdema and passive congestion of the lungs, but there is no mention of pulmonary œdema in the last years of life. This is probably due to the fact that owing to the weakness of the right heart the blood pressure in the lungs was low.

Of further interest is the chronic pancreatitis, a condition not infrequently found at autopsies and unsuspected during life. This did not affect the Islands of Langerhans. The length of time that the individual lived with such marked cardiac disease is unusual. Favorable conditions for him were the absence of arterio-sclerosis and of fibrous myocarditis.

#### OTITIS MEDIA FOLLOWED BY PHLEBITIS AND THROMBUS OF JUGULAR VEIN WITH CONDITIONS CONSEQUENT UPON THIS

**Anatomical Diagnoses.** Otitis media; Purulent mastoiditis; Thrombophlebitis of jugular vein and left lateral sinus; Multiple subcutaneous abscesses; Septic infarction of lung and spleen; Acute splenic tumor; Acute vegetative endocarditis (mitral valve); Cloudy swelling of liver and kidneys; Mastoid operation wound; Streptococcus and staphylococcus infection.

Male, white, age 18 years. Autopsy six hours post mortem. Body of a well-developed, fairly well-nourished boy. Rigor mortis present but not marked. Body still warm. Over the right shoulder and both

elbows are large fluctuating, subcutaneous abscesses. On the left side there is a mastoid operation wound.

Abdomen is normal, free from fluid. Mesenteric lymph nodes are not enlarged.

Thorax. Diaphragm reaches to the fourth rib on the right side; to the fourth interspace on the left side.

Pleural cavities are free from adhesions and contain no fluid.

Pericardial cavity is normal.

Heart, weight 260 grams. Epicardium and myocardium are normal. Endocardium is normal. The aortic, pulmonic and tricuspid valves are normal. On one flap of the mitral valve there are several flattened, sessile, button-like vegetations measuring 2 to 4 mm. in diameter. These are situated near but not at the edge of the flap. On the other flap there is a slightly pedunculated granulation about 3 mm. in diameter and 5 mm. long. These granulations are granular, grayish, somewhat translucent in appearance, and appear to be fairly friable.

Lungs. Surface of both lungs smooth. The lungs are grayish red anteriorly, shading to dark red posteriorly. Cut surface is smooth, moist, and from it a considerable amount of frothy fluid can be expressed. Nowhere can consolidation be made out. In the upper part of the right lower lobe, in the posterior region, there is a grayish yellow area, about 1 cm. in diameter, somewhat irregular in contour, which is visible through the pleura, being situated immediately subpleural. Section of this shows it to be an abscess cavity. No other abscess is to be found in the lungs. The bronchi contain a moderate amount of mucus and show slight hyperæmia. The bronchial lymph nodes are somewhat enlarged, grayish red on section.

Spleen, weight, 410 grams. The spleen does not lie in its usual position just under the edge of the ribs, but lies crowded back where it is bound by quite firm fibrous adhesions; consequently the lower border of the spleen lies well above the costal margin. Near one end there is an area 3 cm. by 4 cm., which is gray in color, and here the tissue is distinctly softer than elsewhere. Section at this point shows a roughly wedge-shaped area whose center is softened and filled with a pinkish gray fluid, and in whose periphery there is a fairly firm tissue of the same color. This is quite sharply marked off from the dark red tissue of the surrounding spleen. At the other end of the spleen there are one or two small areas, none exceeding 1 cm. in diameter, which are lighter, more distinctly yellow in color, and whose centres are soft. Spleen elsewhere is dark red; malpighian bodies indistinct. From the cut surface a considerable amount of pulp is easily scraped.

Stomach, intestine and pancreas normal.

Liver, weight, 1560 grams. Is smooth; brown in color; the markings are indistinct; consistence normal. Gall bladder normal. Kidneys, weight, 370 grams. Capsule strips very readily leaving a perfectly smooth surface. Cut surface of cortex appears to be slightly thicker than normal and is grayish pink in color. The pyramids are darker, grayish red, with indistinct markings; consistence is normal. Adrenal glands normal. Bladder normal.

Aorta normal.

Organs of neck. Continuing the surgical incision down over the sternal notch the jugular vein is laid bare and slit open. At a point about one-half inch above the clavicle the vein contains a gray, purulent material, and to the walls of the vessel is adherent a thin coating of similar color, which cannot be readily stripped off. At the lowest limit of this condition there is a small amount of dark red clot, below which the walls of the vein are perfectly smooth and no clot is present. This condition can be traced up to the jugular fossa, and by removing portions of the temporal bone can be traced into the lateral sinus to a point about on a level with the upper portion of the mastoid sinus. Here the condition ends. Above this the vein contains a fairly firm, dark red clot and has smooth walls. In the mastoid cells there is a small amount of purulent material, the pus everywhere being of this fluid character. The lymph nodes encountered along the course of the vein are somewhat enlarged and grayish pink in color.

Culture made from lateral sinus shows in water of condensation short chains of flattened cocci (streptococci) and scattered round cocci (staphylococci). Surface of serum shows white and yellow colonies of staphylococcus albus and aureus respectively.

**REMARKS.** The case is primarily one of otitis media with extension of the infection to the mastoid cells and to jugular vein producing in this a thrombophlebitis. Such an extension of the infection from the otitis media is one of the dangerous complications which may occur in this affection. The other infections, the acute endocarditis, the subcutaneous abscesses and the septic infarction of lung and spleen are all the result of the following blood infection. Observe the character of the infarction in the lung and spleen. To the mechanical factors produced by the emboli there is added the infection with softening of the tissue. The cultures have shown a mixed infection, the streptococcus is probably the primary agent and the staphylococcus a secondary invader.



A CASE OF ARTERIO-SCLEROSIS WITH FIBROUS MYOCARDITIS  
AND CARDIAC ANEURYSM. DEATH FROM PERITONITIS

**Anatomical Diagnoses.** Extreme coronary sclerosis; Chronic fibrous myocarditis; Cardiac hypertrophy and dilatation; Thinning of a portion of the wall of the left ventricle with slight aneurysmal dilatation; Parietal thrombosis of left ventricle; Thrombosis (embolism) of right common iliac artery and its branches; Amputation of right leg (for gangrene); Hæmorrhagic infarction of both lungs; Chronic passive congestion of liver, spleen and kidneys; Slight chronic diffuse nephropathy; Acute fibrinopurulent peritonitis.

Male, white, age forty-four years. Body well developed, well nourished, 173 cm. long. Rigor mortis present, but slightly developed. Pupils equal, and slightly dilated. Marked pallor of cutaneous surface except dependent parts which show slight lividity. Right thigh has been amputated at the lower third. Transverse amputation wound 5 cm. long, closed by interrupted sutures. Wound shows externally slight evidence of healing, and from it escapes a serosanguineous fluid. In lower half of abdomen is a small puncture wound, closed by collodion dressing.

**Abdomen.** On incising abdomen, there is an escape of a considerable amount of gas having a fecal odor; with this there is marked collapse of the previously distended abdomen. The abdomen contains a considerable amount of greenish-yellow purulent fluid in which float numerous flocculi of fibrin. Three or four hundred cubic centimeters of such fluid were sponged out of the cavity. Peritoneal surfaces are deeply injected; in many places being bright red in color. Adjacent loops of intestine are everywhere interadherent by a sticky, plastic layer of fibrin, separating with moderate ease. One loop of intestine low down in the ileum is quite firmly adherent to the anterior abdominal wall above and to the right of the umbilicus. Separation of this adhesion causes a tear in the intestine which at this point is distinctly friable. Apparently here there is a fairly firm fibrous adhesion, as opposed to the fibrinous adhesions elsewhere. In very many places the peritoneal surface of the stomach, intestines, liver and spleen is covered with a layer of fibrin 1-2 mm. thick, rather elastic, grayish or yellow gray in color, and peeling away fairly easily from the underlying serosa which is brightly injected and smooth. Throughout the large intestine the appendices epiploicæ are congested, often covered with fibrin, and on section show small lobules of yellow fat separated by lines of injected tissue. Here and there the serous surface of the large intestine is covered by flakes of fibrin.

Appendix is free from adhesions, lies in right iliac fossa and its serosa shares the general condition of the other abdominal viscera. The pelvic fossa is more deeply congested than other portions of the abdominal cavity and fibrin is more abundant in this region. Nowhere are there definite walled-off pus pockets. Mesentery is likewise congested. Surface shows here and there exudate, and the mesenteric lymph nodes buried in mesenteric fat are distinctly enlarged, succulent, pink gray on cut surface.

**Thorax.** Diaphragm is not depressed. Both pleural cavities are free from fluid and adhesions. Pericardial cavity free from fluid. Peritoneum smooth and glistening.

Heart is large. Weight, 535 grams. Left ventricle is firmly contracted. Right ventricle is less so. Right auricle is considerably distended. Pericardial surface shows numerous ecchymoses, varying from one to several millimeters in diameter, generally distributed, but very much more numerous along auriculo-ventricular depression and along the descending portion of the left coronary artery. Both coronary arteries can be easily palpated as hard nodular tubes lying beneath the serosa, and their course can be thus traced almost down to the apex of the heart. Left side of the heart contains a small amount of easily separated post mortem clot. Right side of heart contains considerably more of the same kind of clot. Both auricular appendages are entirely free from thrombi as is also the right ventricle. In the left ventricle, largely filling up the apical portion, there is a parietal thrombus measuring 4 by 3 by 1 cm. This is firmly attached to the anterior and right lateral portions of the ventricle from the apex upward. It is ovoid, pinkish gray in color, flecked with small areas of darker red. Its surface is irregularly pitted, but there is no evidence of a portion having recently broken away. Incision into this thrombus shows the central part to be somewhat softened, though still solid in consistency, and much paler in color than the periphery. The post mortem clots described above separate easily from its surface and from the cardiac surfaces, while this is firmly adherent and attempts at removal to tear the clot rather than separate it. Elsewhere the cardiac surfaces are smooth. Valves are normal, except the mitral which shows a few yellow plaques along its base, in nowise interfering with the closing of the valve. Mitral valve 11 cm., tricuspid valve, 12 cm., aortic valve 7 cm., pulmonic valve 7 cm. in circumference, left ventricle 1.3 cm. thick at a point shortly below mitral ring. Right ventricle in a similar place 0.5 cm. thick. Sections made through the ventricle at the point of the attachment of the thrombus show that the wall is here reduced in thickness in places to 0.5 c.m., and instead of the red of the cardiac muscle elsewhere is mottled grayish in color,

leathery in consistency, and in the portion nearest the rhombus is gray without any mixture of red, and this tissue seems to be directly continuous with the thrombus, at least no sharp line of demarkation is apparent, though no bands of tissue can be traced into the thrombus. Sections elsewhere through the wall of the ventricle show scattered areas slightly depressed, red or gray in color, and measuring 2-3 mm. in diameter. Both coronary arteries arise by unobstructed lumina from the aorta, and for a very short distance are smooth. However, almost immediately they become converted into thickened tubes, showing at close intervals irregular nodules of thickening of a grayish yellow color, many of which are calcified and through which a lumen can be traced with difficulty. In many places these nodules occupy one side of the lumen and section of the vessel shows a semilunar rather than a round opening. This condition of extreme sclerosis can be traced in all branches of both coronaries down to their finer ramifications. In none could complete occlusion be made out. There is no evidence of thrombus obstruction, yet the lumen is undoubtedly reduced in many places.

**Lungs.** Surface of both is smooth. Lungs are air-containing for the most part. Posterior portions moderately injected; anterior parts much paler. There is a moderate degree of carbon pigmentation. At the upper portion of the right upper lobe there is a slightly depressed, puckered area from which bands of connective tissue extend a short distance into the lung. No areas of caseation or calcification at this point. In the anterior part of the right lower lobe there is a firm, circumscribed, dark red area 4 by 3 by 2 cm., sharply separated from the adjoining lung.

In the posterior portion of the lower part of the left lower lobe there are similar, less sharply defined, less firm, but solidified areas, dark red in color, and in toto of slightly greater area than the one described in the other lung. Dissection of the pulmonary vessels to these areas reveal small pulmonary arteries occluded by greyish-red, granular, rather friable clots.

**Spleen.** Is somewhat enlarged, dark red in color. Cut surface is dark gray red. Consistency firm. Malpighian bodies are just visible as small grayish points.

**Stomach** is dilated to a moderate degree, and filled with a sour smelling fluid. Mucous membrane appears normal. Duodenum beginning at the pylorus and extending well down below the bile papilla shows closely set foci 1-2 mm. in diameter, of bright red congestion. No other change apparent. Intestinal tract below this appears normal throughout but for the changes already described in the peritoneal surface and which extend for a very short distance into the wall of the intestine.

Pancreas is firm; lobulations distinct. No other change evident.

Liver is slightly enlarged; projects a little below the costal margin of the right mammary line. Its left lobe is proportionately large, and extends somewhat lower than normal in the median line. The surface of the liver is perfectly smooth. The notch of the gall bladder is a little deeper than usual, and the tip of the gall bladder can be seen lying in the notch, projecting a trifle above the surface of the liver. Cut surface of the liver is grayish brown in color. Markings are distinct, centers of the lobules apparently being congested.

Gall bladder is normal.

Kidneys of about normal size. Capsule strips easily from a slightly granular surface; of a dusky gray-red color. Cut surface is of the same dusky hue. Cortex slightly thinned. Markings distinct.

Adrenals normal.

Bladder normal.

Aorta. Beginning from the heart and extending well down into the thoracic region the aorta shows only here and there scattered, yellowish, slightly elevated plaques of thickening. In the lower half of the abdominal aorta the surface is irregularly roughened; here and there are small areas with superficial loss of surface, and in the wall are numerous irregular, calcified plaques. The left common iliac artery shows small scattered areas of thickening, here and there a calcified area. The right common iliac beginning at the bifurcation and extending about 3 cm. is filled with a dark red, nonadherent blood clot. From this point, and as far as can be reached by an interabdominal dissection all branches are filled by blood clot adherent to the walls of the vessel and varying in color from dark red to gray. Central part of this clot is here and there softened and is distinctly friable. In making sections across the vessels at various points a few areas of calcification are encountered in the wall of the vessel, but parts examined do not show any extensive degree of arterio-sclerosis, and the lumen of the larger vessels is certainly in no way obstructed except by the clot.

The renal arteries and the arteries coming off from the coeliac axis are free from blood clot and do not show any evident sclerosis. Their dissection was followed to the spleen, kidneys, and in several branches to the mesenteric border of the small intestine.

The inferior vena cava is not obstructed by clot, and appears normal.

Coverslips and cultures made from the peritoneal exudation gave *staphylococcus aureus*.

**REMARKS.** The right thigh was amputated at lower third for gangrene several days before death. Following the amputation there

was accumulation of gas in intestines for the relief of which puncture was made. The interrelation of the pathological conditions is probably this: There first occurred a general arterio-sclerosis most marked in the coronary arteries and producing calcification in arteries of extremities. Heart hypertrophy due to this and the chronic nephropathy followed. The extreme sclerosis of coronary arteries led to extensive myocarditis, particularly at the apex of left ventricle. Dilatation and production of partial cardiac aneurysm occurred at this point. Owing to the roughening of surface and the slowing of current, a large endo-cardial thrombus formed. In the majority of cases, thrombi form at such places of myocardial dilatation. From this an embolus was given off which plugged the femoral artery on the right side and produced gangrene. This action of the embolus was facilitated by the arterio-sclerosis which prevented compensatory dilatation of the collateral vessels. The wound did not heal and probably became infected. Although the conditions of the autopsy did not permit examination of the leg, it is almost certain that a thrombus was formed in the femoral vein on the same side and from this the emboli which led to the infarctions of the lung were derived. To this was superadded the acute peritoneal infection which followed the abdominal puncture. The autopsy did not show the site of the puncture into the intestine, but this was probably at the point where the intestine subsequently became adherent to the anterior abdominal wall. The small ecchymoses on the pericardium were associated with the infection.

#### SUDDEN DEATH FROM PULMONARY EMBOLISM FOLLOWING THROMBOSIS OF ILIAC VEIN

Anatomical Diagnoses. Operation wounds in both iliac regions; Colon bacillus infection on right side; Thrombosis of spermatic veins; Thrombus of right iliac vein; Embolus in left pulmonary artery.

White, male, age thirty-nine years. Operated on for double inguinal hernia four days before death. Two days after operation increase in temperature with pain in right iliac region. Death occurred suddenly two days later.

Body well developed and well nourished. Rigor mortis is present. Moderate post-mortem lividity. In each inguinal region there is an

incised wound, 8 cm. in length, extending in the direction of Poupart's ligament, and closed by sutures. On opening the wounds, the tissues on the left side are dry and clean, the wound surfaces lightly adherent by fibrin. On the right side the tissues in the wound are bathed in a thin, red, cloudy fluid and the deeper tissues are oedematous. The right spermatic cord is dark red in color, is nodular on palpation and contains fibrinous exudation. In the spermatic veins are adherent, pale red thrombi.

The peritoneum is smooth and glistening. There is some injection of the blood vessels along the lines of incisions, but there is no exudation. The mesenteric lymph nodes are normal. In the right common iliac vein is a light gray-red thrombus, adherent to the wall at one side, and extending upward to 4 cm. above the bifurcation and downward for a distance of 3 cm. into the two branches of the vein. The upper end of the thrombus is capped by a pointed, dark red, soft clot, sharply outlined from the thrombus and easily separated.

The heart is normal in size and in structure. The left pulmonary artery is occluded by a firm, convoluted, non adherent embolus of the same character and of the same diameter as the thrombus in the iliac vein.

The other organs of the body normal.

Smears and cultures from the operation wound on the right side showed colon bacilli.

**REMARKS.** The case is a simple one. The thrombosis of the iliac vein is secondary to infection of the wound on the right side and is due to infection of the vein wall. Thrombi are not infrequent after surgical operations in the peritoneal cavity and may result from congestion and slowing of the circulation without any infection. The embolus was broken off from the thrombus and its lodgment in, and sudden occlusion of, the left pulmonary artery produced sudden death.

**GENERAL ARTERIO-SCLEROSIS, FOCAL IN CHARACTER WITH  
SUDDEN DEATH DUE TO DISEASE OF CORONARY  
ARTERIES**

**Anatomical Diagnoses.** General arterio-sclerosis most marked in coronary arteries of heart; Fibroid myocarditis; Chronic peritonitis with adhesions.

White, male, age forty-eight years. The individual was a man of very athletic habit, a climber of mountains, a skillful swimmer who was accustomed to swim in the sea for hours and who excelled in most athletic

exercises. For two years past has not been able to lead so active and athletic a life as formerly. This particularly felt in exercises which were prolonged. On the day of his death, while engaged in a game of handball, he staggered, leaned for a moment against the side of the court, fell and when his companion reached him he was dead.

Autopsy twenty-four hours after death. The body strongly built, the thorax broad, muscles well developed. General rigor mortis. Some congestion of dependent parts of the body. In the abdomen in the right iliac region is a small cicatrix. The subcutaneous fat small in amount, muscles dark red. In the peritoneum, corresponding to the site of cicatrix in the abdomen, there are numerous fibrous adhesions in the region about the cæcum and appendix. The appendix is 16 cm. long and passes downwards, backwards and upwards beneath the ascending colon, its distal end in the vicinity of the right kidney. It is free for a distance of 8 cm., then passes into a pocket of peritoneum 2 cm. deep, and for the remainder of its length lies entirely in the post-peritoneal tissue. The liver and spleen free from adhesion.

Both lungs free from adhesions. On section deeply congested, no oedema.

The heart weighs 370 grams. The right side is greatly dilated, the left slightly. The valves normal. The myocardium in general of a dark red color, but throughout the left ventricle and in the interventricular septum there are numerous white or pale yellow streaks.

The coronary arteries are of normal size at their exit from the aorta; but in their course show a high degree of arterio-sclerosis which is most marked in the left coronary artery. The sections of the artery show a general thickening of the walls which is intensified in foci where the thickening is lateral. They are free from thrombi or emboli and where thickening is most marked the calibre is very narrow. This condition extends into the smallest branches which can be traced. The situation of the areas of myocarditis correspond to the distribution of the arteries in which there is a marked degree of diseases. The transverse branch of the right coronary artery shows a similar condition. The aorta shows definitely circumscribed, nodular plaques most marked in the arch and thoracic portions. The wall between these plaques shows here and there white or yellow streaks, but is not thickened. A marked degree of focal nodular thickening is seen in the innominate, the sub clavian and carotid arteries. The arteries at the base of the brain are normal. The arteries supplying the abdominal organs show a moderate degree of thickening.

Brain, liver, kidneys, adrenal, intestinal canal and genitalia are normal.

The microscopical examination of the organs with the exception of the heart showed minor degrees of sclerosis in the small distributing

arteries. Sections of the large arteries show very extensive degeneration and rupture of media with great thickening of the corresponding intima. The most marked degree of degeneration is found in the coronary arteries of the heart. Where the nodular thickening is most marked there is complete destruction of media. Examinations for fat showed very marked fatty degeneration everywhere.

**REMARKS.** The weight of the heart, 370 grams, is somewhat above the average, but is normal for an individual leading a very athletic life. It is not improbable that the arteriosclerosis of the coronary arteries interfered sufficiently with the nutrition of the heart to produce some loss in reserve force, some time previous to death. In the present condition of the coronary arteries it is probable that the nutritive reserve of the heart was seriously diminished. The areas of fibrous myocarditis show that in places complete destruction of myocardium with substitution of fibrous tissue has taken place. The sudden death is to be attributed to the instant exhaustion of the imperfectly nourished muscular tissue. The arterio-sclerosis is unusual in the extent of the lesions and in their marked focal character particularly those in the aorta. There is no indication of syphilis. The small arteries of the body are in good condition, though occasionally an artery is found as in one of the arcuate arteries of the kidney which shows a condition similar to that in the aorta. The cicatrix in the abdominal wall is the result of a previous operation, for, but without resulting in, appendectomy.

#### HEART HYPERTROPHY WITH ENDOCARDIAL THROMBI, ARTERIO-SCLEROSIS AND CHRONIC NEPHROPATHY

**Anatomical Diagnoses.** General arterio-sclerosis; Thrombosis of coronary artery with infarction of heart; Heart hypertrophy and dilatation; Multiple mural thrombi in heart; Chronic diffuse nephropathy with recent and old infarction; Pulmonary embolism and infarction; Healed pulmonary tuberculosis; General passive congestion; Edema; Ascites; Hydrothorax and hydropericardium.

Male, white, age fifty years. Body that of a short, well built, rather stout man. Subcutaneous fat fairly abundant. Lymph nodes not palpable. Rigor mortis. There are about 15 or 20 discrete red papules



1 to 2 mm. in diameter scattered over the anterior chest. (Small capillary telangiectases.) Slight post mortem lividity. Slight oedema of lower extremities. Abdomen distended.

Peritoneum. Subcutaneous tissue somewhat oedematous. The peritoneal cavity contains about 300 c.c. of pale, clear fluid. Peritoneum smooth. Stomach and intestines distended.

Pleuræ. Both internal mammary arteries are thickened. Each pleural cavity contains about 700 c.c. of pale amber fluid. There are dense, thick adhesions over the apex of the right lung.

Heart. The pericardium contains 50 c.c. of clear, pale fluid. No adhesions. The heart is large, weight, 770 grams. The right auricular appendage is entirely filled with a pale red friable adherent thrombus. Similar small adherent thrombi are found over interventricular septum in right ventricle between the muscle bands. These thrombi present much variation in color and in character. Some of them are red, others, on section, red and white, and others entirely white; the centres of some of the larger white thrombi are softened.

The aortic cusps show a moderate thickening of their free margin and a small calcareous nodule occupying the position of the corpus arantii of one of the cusps. The coronary arteries show advanced sclerosis and calcification. The lumen of the descending branch of the left coronary artery is occluded 2 mm. from its origin by a dark-brown friable adherent thrombus. Beyond this the inner half of two-thirds of the posterior wall of the left ventricle is darker than the surrounding myocardium and contains large pale or grayish-yellow areas, most numerous and distinct immediately beneath the endocardium. The papillary muscle attached to this region is soft, pale yellow and its base is surrounded by mural thrombi.

The aorta shows extensive arterio-sclerotic thickening both in patches and diffuse. In the abdominal aorta most marked above the bifurcation there is extensive calcification and a number of ulcers with irregular undermined edges. All the large arteries show marked diffuse and nodular sclerosis.

Lungs. At the apex of the left lung the pleura is thickened and puckered. On the surface adjacent to the pericardium there are a number of small grayish or yellow, firm nodules 1 to 2 mm. in diameter, gritty on section with cheesy centres. These lie just beneath the pleura. On section the lung is of a diffuse brick red color and considerable fluid oozes from the cut surface, but the tissue is crepitant throughout. At the apex of the right lung is a large nodule 2 cm. in diameter, the centre containing a grayish-yellow material of the consistency of putty; around this there is a dense fibrous capsule with fibrous extensions into the sur-

rounding lung tissue. The pleural surface around the nodule is thickened and cicatricial. The entire lung is heavier, more congested and contains more fluid than the left. On the posterior surface of the lower lobe there is a solid area 4 by 3 by 2 cm. sharply separated from the adjoining lung tissue, which, by comparison, is deeply depressed below the level of this area. The area is dark red in color. The cut surface is smooth and dark red in color, and sharply separated from the adjoining congested lung tissue. In shape the area is triangular, the base on the pleural surface. The pulmonary artery leading to this area is occluded by an adherent pale red embolus. The bronchial lymph nodes are enlarged, deeply pigmented and injected and contain caseous and calcified masses.

Liver, weight, 1515 grams. Surface deep brown, slightly irregular, and finely mottled with dark and paler areas. The cut surface shows this nutmeg mottling more plainly.

Spleen, weight, 150 grams. Surface dark red and slightly wrinkled, consistency increased. Malpighian bodies and trabeculae prominent.

Pancreas normal.

Kidneys, weight, 330 grams. Adherent to perinephritic fat. Capsules nonadherent. In each kidney beneath the capsule there are a few depressed areas from 0.5 to 1 cm. in diameter with yellow centres. These show on section a grayish-red cicatricial periphery sharply separated from the yellow centres. In the lower pole of the left kidney is a slightly elevated, pale yellow area 2 by 2½ cm. with an irregular and intensely red border. On section the area is firm, rather dry, irregularly triangular in shape, the apex slightly extending into the pyramid. On the kidney section the arterial branches are prominent. The cortex is somewhat reduced in size, the consistency increased, the markings obscure.

Adrenals normal.

Genitalia normal.

Gastro-intestinal tract. Mucosa of stomach and intestines deeply injected.

Brain and cord not examined.

The microscopic examination of all the organs shows advanced arteriosclerosis most marked in arteries from ¼ to ½ mm. in diameter. In many of these there can be seen only traces of the media, the greatly thickened wall being formed by intima only. The heart shows, apart from the area of infarction, a general and diffuse fibrous myocarditis. The infarcted area shows necrosis and fragmentation of the muscle fibres and infiltration with polynuclear leucocytes.

Throughout the liver the cells in the centres of the lobules are in part necrotic, in part they have wholly disappeared and in their place there is extensive hæmorrhage.

**REMARKS.** The case presents a variety of conditions some of which are closely interrelated. There is an old tuberculosis of the lungs, the length of time since the infection indeterminate. The lesions have become completely enclosed in cicatricial tissue and there has been extension to the bronchial glands only. The heart hypertrophy is to be referred to the chronic nephropathy and arterio-sclerosis, the tripos being a common one. The extensive formation of thrombi in the heart is associated with the dilatation, the diminished rapidity of flow, the increased irregularity of the surface and the effect of the myocarditis. The arterio-sclerosis of the coronary arteries which is the cause of the myocardial degeneration is a part of the general arterial disease. The emboli in the lung came from the thrombi in the right side, and the infarction following the embolus is due to the increased pressure in the pulmonary veins produced by the dilatation of the left heart and relative mitral insufficiency. The infarctions in the kidney result from embolism of branches of the renal artery. The increased venous pressure has led to an increase in the tissue fluid shown by the oedema and the accumulation of fluid in the body cavities.

#### CASE OF ANEURYSM OF ARCH OF AORTA WITH RUPTURE

**Anatomical Diagnoses.** Aneurysm of ascending arch of aorta with rupture; Erosion of sternum; Hæmorrhage into subcutaneous tissue with rupture through skin; Hæmorrhagic infiltration of tissue of anterior chest wall.

Male, white, age fifty-two years. Body well developed, well nourished and muscular. Rigor mortis. Slight post mortem lividity. In the median line on the anterior surface of the chest is a hemispherical swelling, which projects 11 cm. above the body surface and has a circumference at the base of 40 cm. The surrounding skin for a distance of 5 to 10 cm. is oedematous. The skin from the anterior borders of the axilla and the root of the neck as far down as the umbilicus is yellow, with slight greenish tinge. The surface of the tumor-like swelling is irregular and knobby. Just to the right of the median line there is an irregular opening and below this a smaller opening from both of which a soft red blood clot projects. The subcutaneous tissue of the chest and upper abdomen is irregular, infiltrated with blood and fibrin.

**Peritoneum.** Surface smooth and glistening. The left lobe of the liver is adherent to the diaphragm by loose, tough, fibrous bands. The

intestines are pale and distended with gas. (The sternum is disarticulated, the trachea and œsophagus cut across, and the thoracic contents with the sternum and aorta removed in mass.) The aorta opened posteriorly shows a few yellowish patches in abdominal portion, and considerable sclerosis about the origin of the cœliac axis. In the upper 9 cm. of the thoracic aorta there is marked sclerosis and calcification, chiefly on anterior surface, and above this the surface is irregularly thickened with cicatricial wrinkling and with but little calcification. The great vessels given off from the arch are in high degree sclerosed and have small flat areas of calcification on the surface. The aorta from a point  $1\frac{1}{2}$  cm. from the aortic valve to the origin of the left subclavian forms a large aneurysmal sac, 20 cm. in circumference. The inner surface of this is irregular and contains numerous yellow-white calcareous plaques. The sac anteriorly is adherent to the sternum from the lower border of the first rib downward to about the middle. The inner surface of the sternum is extensively eroded and completely destroyed over an area 6 cm. in diameter, where it is replaced by a dense fibrous tissue, forming the anterior wall of the aneurysm. In this there is an opening 2 cm. in diameter forming a communication between the cavity of the aneurysm and a large cavity beneath the skin filled with coagulated blood. All the tissues of the anterior chest wall are infiltrated with blood and in several places these are distinct cavities filled with clots. There is also a large hæmorrhagic infiltration of the pleura between the first and second rib.

**Heart.** The pericardial cavity in places is obliterated by adhesions. The heart slightly enlarged, the valves normal.

The lungs and other organs of the body unimportant.

**REMARKS.** There is marked arterio-sclerosis, chiefly of arch and thoracic aorta and of the large arteries given off from arch. The aneurysmal dilatation is fusiform and involves the entire circumference of the aorta, but the chief dilatation is of the anterior wall. With the continuing enlargement it came in contact with the sternum and adherent to this around the area of contact. The arterial wall in contact with the sternum and the periosteum became necrotic and absorbed, the exposed sternum forming a part of the cavity of the aneurysm. The bone also disappeared under the pressure and pulsation of the aneurysm, the anterior wall of which was then formed by the periosteum and fibrous tissue. This also gave way allowing the aneurysm to perforate into the subcutaneous tissue, forming a large hæmorrhage in which the blood coagulated.

The new cavity gradually grew by the continued hæmorrhage, the skin became perforated, allowing external hæmorrhage, and there was also hæmorrhagic infiltration into the surrounding tissue.

ANEURYSM OF THE ABDOMINAL AORTA WITH EROSION OF  
VERTEBRÆ

Anatomical Diagnoses. Arterio-sclerosis; Aneurysm of abdominal aorta with occlusion of abdominal arteries.

(Only that portion of the autopsy protocol relating to the aneurysm is quoted.)

Death was due to infection following operation for appendicitis.

Male, white, age thirty-nine years. Body that of a well-nourished, well-developed and powerfully built, tall man, 182 cm. in length. Rigor mortis complete. Post mortem lividity marked. After removal of intestines a tumor mass is found lying upon the vertebræ and bordered on each side by the crura of the diaphragm.

Heart, weight, 350 grams, myocardium firm, valves and endocardium normal. Coronary arteries show an occasional soft yellow patch. The beginning of the aorta is thickly studded with small elevated, white and yellow areas without calcification.

The aorta is continuous above and below with the tumor mass in the abdomen which lies over the lower dorsal and upper two lumbar vertebræ and is included between the crura of the diaphragm. The aorta is removed by stripping from the vertebræ as far as possible from above and below until it became firmly adherent to the vertebræ. These vertebræ were then sawn through and the aorta opened from behind by means of the incision through the vertebræ. Over the twelfth dorsal, first and second lumbar vertebræ is an aneurysm sac 14 cm. long and 13 cm. in its greatest diameter. The first and second lumbar vertebræ are excavated for a depth of 2-3 cm. The articular fibro-cartilages are only slightly eroded and project between the eroded vertebræ. The cavities in these two vertebræ are filled with firm grayish-red clot. The general shape of the sac is fusiform, and at the level of the first lumbar vertebra a second sac 3 cm. deep and 4 cm. in diameter is given off from the anterior wall of the main aneurysm. The main aneurysm contains but a small amount of fibrin most of which lies against the vertebræ where the eroded bone forms the posterior wall. The small sac contains fresh dark red clot. The aorta above and below the aneurysm and the aneurysm wall is thickly covered with corrugated, elevated white and yellow patches which are more numerous above the aneurysm than below.

There is no calcification. The common iliac arteries are very slightly sclerosed, the left has one patch only, the right several patches. The inferior mesentery and renal arteries are patent. At the orifices of the left renal artery is a conical bulging of the aneurysm wall about 1 cm. in diameter and depth. Where the phrenic and coeliac axis and superior mesenteric arteries are given off from the aneurysm they are occluded by firm, friable, grayish clots.

**REMARKS.** The aneurysm is given off from the posterior portion of the abdominal aorta. In this case, the bodies of these vertebræ are eroded as was the sternum in the preceding case. The intervertebral fibrocartilages are extremely resistant to the process and stand out between the bodies of the eroded vertebræ. The aneurysm is evidently fusiform, the whole wall of the artery being involved in it. Although the wall of the aneurysm is often irregular, it is rather uncommon to have a secondary aneurysm formed in the aneurysmal wall as in this case. The aorta shows an extensive arterio-sclerosis without calcification, in type resembling the syphilitic form, but does not resemble this in the extent of the area involved. Notice that there is no heart hypertrophy.

#### A CASE OF SACULAR ANEURYSM OF THE ARCH OF THE AORTA

**Anatomical Diagnoses.** Aneurysm of the arch of the aorta; Erosion of the sternum; Hydrothorax; Obliteration of lumen of appendix with cystic dilatation; Chronic pleurisy; Compression atelectasis of lung; Bronchopneumonia; Arterio-sclerosis of aorta; Bronchitis.

Negro, male, age sixty years. The body large, strongly built, greatly emaciated, the abdomen retracted. Subcutaneous fat small in amount and yellow. Muscles wasted, thin and red. All tissues remarkably dry.

The appendix long, its tip attached to rectum. The distal one half of the appendix is dilated, the proximal contracted. It is surrounded by adhesions. On section there is complete obliteration of the lumen up to the dilated half. The average diameter of the dilated distal half is 2 cm. This is filled with clear, mucoid material, its mucous membrane thrown into folds.

The costal cartilages are ossified. The sternum is thin, the bone porous, easily crushed. The entire anterior mediastinum is filled with a large tumor mass extending to the left side. This mass is adherent to the sternum and which is eroded over the surface of contact. With the

exception of the condition in the vermiform appendix, no lesions are found in the abdominal organs save a well-marked chronic passive congestion.

**Pleura.** Left side of the chest is filled with bloody fluid. The right is dry. The left lung is retracted and adherent to the chest wall by dense, long drawn out adhesions. Where these adhesions are attached to the lung, this projects in long papillary masses. The lung is adherent to the pericardium, to the tumor mass and to the vertebra, and so reduced in size that the entire organ forms a mass not much larger than the closed fist. The entire pleural surface is covered with a thick, red granular membrane. On section the lung is completely solid with a creamy exudation exuding from the bronchi and from the compressed lung tissue. On section of the right lung an abundance of muco pus can be squeezed from the bronchi. Smears from this pus show a variety of organisms, diplococci in pairs conforming morphologically to pneumococci predominating.

The pericardial cavity obliterated by firm adhesions.

The heart is somewhat dislocated downward and to the left. It is of normal size, myocardium and valves normal.

The tumor mass in the anterior mediastinum is formed by an aneurysm springing from the antero-lateral side of the ascending aorta just before the origin of the innominate. The superior inferior diameter of the aneurysm is 15 cm., the antero-posterior is 13 cm. It extends more on the left side of the median line and has sharply compressed the vessels at the root of the left lung. The opening into the aneurysm is oval, the average diameter of this is 4 cm. The edge of the opening is perfectly smooth. The aneurysm is filled with dense laminated fibrin and fresher clots.

The ascending, transverse and thoracic aorta is thickened, the cicatricial tissue showing nonelevated white opacities and small partially elevated plaques. There is but little arterio-sclerosis in the remaining arteries.

**REMARKS.** This is a good example of the sacular aneurysm. There is a general condition of arterio-sclerosis, but the condition especially favoring the aneurysm formation existed at a circumscribed area which gave way. The large tumor mass which was so formed has pressed against the sternum, producing a slight erosion of the bone. The very extensive hydrothorax on the left side is probably to some extent due to the compression of the veins at the root of the lung by the aneurysmal tumor. The lung was adherent to the pleura by dense adhesions before the formation of fluid in

the pleural cavity began. These adhesions have stretched to a large extent, but have drawn out the tissue of the lung in masses at the point of attachment. The fibrinous exudation on the surface of the lung has become completely organized with the formation of a red granular membrane. The lung has also been the seat of a chronic infection with probably an acute following. The condition of the appendix is interesting. There has been here a primary acute appendicitis with destruction of the mucous membrane and obliteration of half of the lumen. In the distal half there has been a continuous secretion of mucus from the mucous membrane which has accumulated, forming a cyst of the appendix. Cysts of the appendix so produced may attain a considerable size, even up to 6 or 8 cm. in diameter.





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## GROWTH, HYPERTROPHY, HYPERPLASIA, REGENERATION

New formation of cells and tissue is, as we have seen, one of the most constant phenomena in inflammation and it is by means of this that the injury to the tissue is repaired. The new formation of cells takes place by indirect or mitotic nuclear division. The complicated process of this division makes it possible for the new nuclei to have parts of all the chromatin of the old nucleus. Direct division of nuclei may take place in degenerated cells of the tissue, but save in tumor cells, it does not lead to new cell formation. After the application of a caustic to the centre of the cornea such direct nuclear division without new formation of cells and without cell growth may be seen in the swollen and degenerated cells around the site of injury, and not infrequently in degenerated epithelial cells, groups of nuclei may be seen. A similar multiplication of sarcolemma nuclei attends many of the forms of muscle degeneration. In this process there is no increase of chromatin preceding the division and the new nuclei have but little and irregularly distributed chromatin.

Most tissues in the body possess a capacity for growth which differs in degree in different tissues. In those tissues in which growth constantly takes place, as the blood and cutaneous epithelium, the growth capacity is greatest. It can be active also in those tissues in which there is the least degree of cell differentiation as in the endothelium and the connective tissues. It has been shown recently that growth of cells will also take place outside of the body when the environment is suitable.

One of the causes assigned for new cell formation after injury is that, by the disturbance of tissue relations and equilibrium, the restraint to growth which the cells mutually exert upon each other is removed. This theory assumes that growth is not due to a stimulation of the formative capacity of cells, but that the formative capacity, always active, is held in check by a restraining influence of adjoining cells. There is no doubt that the surest way to excite cell proliferation is the production of loss of substance. The growth takes place not only from the cells in the immediate vicinity

of the loss, but in cells at a distance, the most striking instance of this being the new formation of the leucocytes in inflammations. This may be thought of as similar in character to the tissue growth around an injury. The withdrawal of the leucocytes from the blood, the hypoleucocytosis, destroys the blood cell equilibrium, i.e. the relative proportions in the numbers of leucocytes, which is restored by proliferation in the blood tissue in the same way that loss of epithelium or connective tissue cells is made good by proliferation of adjoining cells. Such a regulating mechanism of growth must be more than the mere physical contact of cells, and its action must be by chemical agencies. It is possible to think that each tissue in the body may produce substances which stimulate or restrain the formative capacity of cells and that the normal equilibrium of the tissues is due to the interaction of such substances. That chemical substances of the nature of hormones can excite growth in organs is evident both in physiology and pathology, instances being the growth of the mammæ in pregnancy and the abnormal growth of the extremities in pathological conditions of the hypophysis. By the injection of Scharlach R. into the subcutaneous tissues, an active growth of the adjacent epithelial cells can be produced. In case of the blood formation chemotactic substances from the inflamed area may enter into the blood and in consequence of their action the leucocytes already formed in the marrow enter into the blood producing an actual loss of substance in the marrow tissue. The examination of the marrow shows that the first change following hypoleucocytosis is the withdrawal of the stored leucocytes of the marrow and this is followed by proliferation. In the course of many of the infectious diseases new formation of cells takes place, not only in relation to the local injury produced by the bacteria, but remotely, due to the action of toxic substances brought to the tissues by the blood. One of the most common conditions in infections is the production of phagocytic cells in the liver by proliferation of the endothelium of the capillaries. The action of phagocytes in certain cases seems to be a mode of restoring the cell equilibrium when in an area there is an excess of cells of the lymphoid type.

**HYPERTROPHY AND HYPERPLASIA.** By *hypertrophy* is understood increased size of an organ due to increased size and increased functional capacity of its essential elements, whereas by the term

*hyperplasia* a numerical increase is indicated. No sharp line can be drawn between these processes; in certain organs the increase in size of the elements, in others the numerical increase, is the dominant factor. Increase in size of an organ is not identical with hypertrophy, but may accompany atrophy, as is seen in degenerated muscle in which there often is a large formation of interstitial fat, and in emphysema of the lungs in which the air cells are dilated and lung tissue reduced in amount. The best examples of hypertrophy are seen in the increased thickness of the muscular walls of hollow organs when there is obstruction in their outlet. The wall of the left ventricle may increase to more than double its normal thickness when there is obstruction at the aortic outlet and the wall of the bladder greatly hypertrophies in cases of stricture of the urethra. Such hypertrophy is similar in its general character to the muscle hypertrophy produced by exercise. There is a close relation between the functional, nutritive and formative capacity of cells. The increased exercise of function brings about increased blood supply and more active nutritive changes, and under such conditions the formative activity may also become stimulated. Whether the formative activity leads to hypertrophy or to hyperplasia depends upon the nature of the tissue. It is doubtful if there is any increase in the number of fibres in the hypertrophy of the voluntary and cardiac muscle. In the hypertrophy of the muscular coats of the intestine above a stricture there is numerical increase with the enlargement; in the hypertrophy of the uterus during pregnancy there is great enlargement of fibres without increase in number. In glandular organs enlargement of the glands cells takes place to but a limited extent. Hypertrophy of an organ will not take place when, in consequence of disease, the conditions for increased nutrition are not favorable. The hypertrophied organ is not a normal organ. The range of conditions to which the normal organ can adapt itself by an increase of function is diminished, and the capacity for growth diminishes with its exercise. If the demands made upon the hypertrophied heart continue to increase, a time comes when the organ seems incapable of further hypertrophy. In addition to increased size and number of elements there usually are other morphological changes shown by a relative increase in connective tissue and in abnormal relation between nucleus and cytoplasm.

In the case of paired organs removal of one will, in some cases, lead to hypertrophy of the other, — compensatory hypertrophy. When one kidney is removed the other will enlarge, and the single organ can then perform the work of the two. In this enlargement the tubules become larger and longer than normal; there is an increased formation of epithelial cells, an increase in the size of the glomeruli, but no new formation of tubules or glomeruli. In the case of organs more or less closely related, hypertrophy of one may take place on the removal of the others. Thus, after removal of the thyroid the hypophysis may hypertrophy. In the case of paired organs in which there is not constant but periodic function, such compensating hypertrophy does not take place or takes place to but a limited extent. Nor does this hypertrophy take place in the lung. The removal of one lung may produce an excessive enlargement of the other, but the condition is rather that of emphysema rather than a true hypertrophy. Compensatory hypertrophy takes place readily in the related tissues of the lymphatic apparatus.

**REGENERATION.** By this is understood a new formation of tissue to take the place of a loss, the new tissue having the same structure and function as that which was lost. To what extent cell destruction followed by regeneration takes place in the normal tissues is uncertain. In the covering epithelium both of the exterior and interior surfaces there is constant cell loss which is made good by new formation. As evidence of this, nuclear figures always are found in the malpighian layer of the skin and in the intestine; in the latter, the new cell formation takes place almost exclusively in the crypts. In the blood there is constant cell destruction and regeneration shown by nuclear figures in the marrow and lymph nodes. In the normal glandular organs nuclear figures are extremely uncommon except in conditions of great functional activity.

There are certain general laws which seem to apply to regeneration. The less complicated the structure of an organism, the greater is the power of regeneration. It is most perfect in the unicellular organisms and decreases with complexity of organization. In the single organs regeneration is less perfect the greater the functional differentiation of cells and the greater the complexity of architectural structure. Regeneration may be active in the single cells of a tissue, but in the new growth the perfect inter-

relations of tissue may not be restored (repair). The younger the animal the greater the power of regeneration.

In the central nervous system there is no power of regeneration. There is not only a greater degree of functional differentiation of the ganglion cells than in other cells, but the architectural structure of the tissue is so complicated that a new formation of tissue with the re-establishment of the intricate relations of cells and fibrils would seem impossible. Although there is no regeneration in the central nervous system, there is great regenerative power in the peripheral nerves. After section of a nerve, the entire peripheral portion degenerates and there is degeneration of the central end up to the nodes of Ranvier. In the process of regeneration the axis cylinders grow out from the central end and attain a peripheral distribution, this taking place more readily if they can gain access to the degenerated peripheral end. Only the axis cylinders grow out in this way, the sheath of Schwann being formed peripherally.

In the skin, regeneration of the covering epithelium quickly takes place, but when there is destruction both of skin and papillary layer, the papillæ are not at all or are imperfectly regenerated. If in smallpox the destruction of tissue involves the papillary layer, a smooth scar results. When the skin glands and other epidermic structures are destroyed they are not regenerated. In the scar resulting from a healed ulcer there are neither hairs, sebaceous glands, nor sweat glands. Much the same thing is true of the alimentary canal. There is great power of regeneration of a loss confined to the epithelium, but new formation of villi does not take place and the newly formed simple glands are very imperfect. The healed typhoid ulcer shows a smooth surface covered with epithelium but without villi and with the glands represented by a few irregularly distributed short tubules.

Such complicated glandular structures as the mammary and salivary glands, in which there is epithelial differentiation into secreting epithelium and ducts, have slight capacity for regeneration. The new formation of epithelial structures proceeds rather from the less perfectly differentiated ducts than from the secreting cells of the alveoli, and the new tissue is imperfect. In the liver, on the other hand, there is greater regenerative capacity than in any other organ of the body. It is possible to produce by chloroform poisoning necrosis of cells in the centre of the lobule extending

half way to the periphery, and in four days after this to have the lost tissue so completely and perfectly reproduced that there is no microscopic evidence of the former destruction. The liver, however, in the relations of cells and vessels is one of the simplest epithelial structures in the body. After chloroform necrosis the cells around the injury multiply rapidly as is shown by numerous mitotic figures and the new cells extend along the capillary framework which remains intact. Necrosis of single cells often occurs and may be produced experimentally, and new cells are quickly formed. Where there is more extensive destruction, involving also the architecture of the organ, regeneration takes place both from the liver cells and by growth of the bile ducts with differentiation of their cells into liver cells. Under such conditions the newly formed tissue is not a complete reproduction of the old, the lobules being larger, less perfect in structure, and there is increase in the amount of connective tissue.

In the kidney there is not complete regeneration of lost tissue; neither new tubules nor glomeruli are formed. The loss of single epithelial cells is made good by proliferation of the adjoining cells, if the integrity of the tubule as a structure is preserved. The glomeruli and tubules can undergo compensatory hypertrophy in the single organ, just as in the remaining kidney after removal of its fellow. In kidneys in which there has been considerable destruction, glomeruli much larger than normal may be found and single tubules may become enlarged and elongated. In the ovary and testicle there is no power of regeneration of the sexual cells. Any growth which results comes from the interstitial tissue.

Regeneration of striated muscle is very imperfect. There is no complete new formation, but there may be an imperfect growth from the severed ends of fibres. After degeneration of muscle, large cells may be seen within the sarcolemma which have been considered sarcoblasts. It is more probable, however, that these are merely phagocytic cells and concerned, not with muscle formation, but with the removal of degenerated tissue.

The regeneration of bone is complex; it does not take place from the old bone but by means of the formation of a cellular tissue from the periosteum, and to a less extent from the endosteum, in which bone develops as in the embryo. In this germinal tissue a network of bone is formed by means of a homogeneous intercellular sub-

stance which at first is imperfectly calcified and in which the forming cells become the future bone corpuscles. In this tissue, islands of cartilage are often formed by the production of a hyalin intercellular substance which contains chondrin, and from this tissue bone formation can proceed. New vessels growing out from the old are abundant and about them myeloid tissue may appear. The new formation of bone is very abundant; in a fracture it extends to a considerable distance beyond the fractured ends and serves as a temporary splint. It is gradually absorbed by the phagocytic osteoclasts and a more compact bone replaces it. No regeneration in cartilage takes place by growth of the cartilage cells. As in bone, a germinal tissue is formed from the perichondrium within which new cartilage is produced.

**METAPLASIA.** This is the production of specialized tissue from cells which normally produce tissue of another sort. In regeneration it was seen that the new formation of tissue takes place from tissue of a similar character. The most striking example of metaplasia is the formation of bone in parts which normally do not contain bone. Bone may be formed under pathological conditions in the choroid of the eye, in the lungs, in the heart valves, arterial walls, in the kidney, and in other places. In such bone, marrow spaces and marrow may be found. Cartilage also may form in places where it is not normally present. The various epithelia of the body also afford instances of metaplasia. Chronic ulcers of the trachea may heal by the formation of squamous epithelium on the surface. If the inner surface of the bladder or of the uterus be exposed to an irritating environment, the new epithelium takes the character of epidermis; in chronic inflammation of the gall bladder the same is true. Cartilage may disappear in an immobilized joint and be replaced by connective tissue. In none of these cases is there a conversion of one tissue into another, the metaplastic tissue being newly formed. There is a limited range only of such metaplasia; it occurs in tissues nearly related and of the same embryonic origin, and does not occur in tissues of complex structure. One epiblastic or hypoblastic tissue can be converted into another epiblastic or hypoblastic tissue, but mesoblastic tissue is not converted into epiblastic or hypoblastic and vice versa.





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130d

## TUMORS

A tumor is a new formation of tissue which in growth, in structure, and relations departs to a greater or less degree from the normal type of the tissue to which it is related in structure or origin, and from all other forms of pathological growth. It is an autonomous structure growing in the body as a parasite, and its growth capacity is unlimited. The human body is an organism, and the various tissues and organs of the body are not independent entities but show an intimate relation of all parts with the whole. There is every reason to believe that this interrelation and coördination, this control and direction of all the activities of the tissues, is, in great part at least, effected by means of substances called hormones or chemical messengers which are produced as one form of internal secretion in the ductless glands and in other organs of the body. The capacity of the tissues for growth varies with the tissue and with age and it may be stimulated in various ways. The growth, however, in its main characteristics is purposeful and subordinated to the organism. A tumor cannot be considered as an organ of the body, its activities not being coördinated with the organism. It is a part of the body, but it is rather to be considered as a wild and lawless guest not influenced by, or conforming with, the regulations of the household. In the capacity for growth the cells of tumors can be compared rather with plant than with animal cells. The rapidity of growth varies, certain tumors for years showing but little increase in size, others being seen to increase almost from day to day. The growth is often intermittent, periods of quiescence alternating with periods of activity. The nutrition and growth of a tumor is but little influenced by the condition of nutrition of the host. Very rapid growth may be seen in conditions of extreme malnutrition and emaciation of the host.

IN SIZE, a tumor may be microscopic, or it may exceed the weight of the individual who bears it. The limitations to its growth are external and not internal. There is no distinctive color to a tumor. Certain tumors have color which depends upon the presence of

definite pigments produced by the tumor cells, such as the brown or black pigment of the melanotic sarcoma and the green pigment of the chloroma. There also may be considerable amounts of hæmatogenous pigment, the remains of hæmorrhages which have taken place. Usually tumors have a gray color modified by their varying vascularity, with the appearance also of whitish and more opaque areas due to variations in the amount of fat in the cells. There is every variation in consistency, from that of a tissue so soft that it can easily be pressed through the fingers to a consistence of stony hardness. The shape of a tumor depends upon its nature, manner of growth, and situation. When it arises near a surface it may project from a pedunculated attachment; both in this situation and within the tissues it may be round or lobulated or irregular, the shape being influenced by the varying opposition of surrounding tissues to its growth.

**STRUCTURE.** Like other tissues, tumors are composed of cells, intercellular substances, blood vessels lymphatics and rarely nerves. No general description can be given of the cells of tumors, there being too much variation in relative numbers, in size, structure and relation between nucleus and cytoplasm. The energies of the cells in tumors are almost exclusively directed towards growth and nutrition and there is some correspondence between the growth of tumor cells and rapid cell growth in other conditions. As in normal tissue, growth takes place by cell multiplication which usually is preceded by mitosis. Direct nuclear division, division by nuclear budding and by complicated multiple mitoses, also occurs. From continued growth without division enormous cells containing large and irregular nuclear masses may be seen. In certain tumors the presence of giant cells with multiple nuclei form so distinguishing a feature as to affect the nomenclature (giant cell sarcoma). Tumor cells very frequently contain fat. Glycogen may be found within them, as well as hyalin masses which give no definite chemical reaction and which are often enclosed in vacuoles. Chromatin granules cast off from the nucleus, assuming various forms and often associated with the hyalin substances, are often present. In certain tumors the cells seem to be amœboid; on the warm stage slow amœboid movements have been seen, and in rapidly fixed tissues we may find cells in shapes and positions which we are accustomed to associate with amœboid

activity. Phagocytosis may occur, but is not a prominent characteristic.

**THE INTERCELLULAR SUBSTANCES** have a varying relation. In certain cases they are produced by the tumor cells and form an integral part of the tumor; in other cases, especially in the epithelial tumors, there is a definite separation between the actively growing cells which give the tumor its characteristics and a connective tissue stroma which bears the blood vessels and forms a framework supporting the cell masses. Such a stroma is a growth coming from the host, secondary to and dependent upon the growth of the epithelium, comparable to the connective tissue growth in developing organs of the embryo.

**THE BLOOD SUPPLY** of tumors varies with the character of the tissue and the rapidity of growth. Blood vessels are abundant in the rapidly growing tumors, the reverse in the slow. They grow with the tumor and come from the adjacent blood vessels of the host. They may enter the tumor from a single point, but usually, as the tumor enlarges, new vascular connections are formed. The vessels of the host which provide the nutrition of the tumor enlarge with its growth. The blood vessels are irregular, and there is not always the definite differentiation into arteries, capillaries and veins as in the normal tissues. The vessels often have the character of large thin-walled capillaries with an irregular lumen; often they are mere channels with only a layer of endothelial cells separating the blood from the tumor cells. In such a condition disturbances in the circulation from the pressure of the growing tissue on the vessels are common, with resulting necrosis, infarction or simple hæmorrhage. Very little is known regarding lymphatics in tumors. Spaces lined with endothelium are often seen, and lymphatics have been shown by injection. They evidently grow into the tissue with the blood vessels and there is no reason to believe they are less abundant in tumors than in normal tissues. Nerve fibres have been described in the stroma and in certain cases they represent an integral part of the tumor.

**ORIGIN.** A tumor arises by the cells of a certain part proliferating and taking on the characteristics of a tumor. No one has ever seen the beginning of a tumor nor would it be possible to recognize a small area of proliferating cells as a tumor. It is impossible to say whether the beginning is from a single cell or a

group of cells or an area of tissue. When the tumor arises it continues to grow by the proliferation of its own tissue. The adjoining tissue of the same character may, to some extent, merge with the tumor and form a part of it. It is only in epithelial tumors that this apparent change in the adjacent epithelium is seen; in most tumors it is certain that there is no transformation of adjacent tissue into the tumor. A tumor may have several centres of origin which in the further course of development become merged into a single growth.

The growth of the tumor may be: (1) simply expansive, pushing aside the tissue with which it comes in contact, the connective tissue forming a capsule around it as around a foreign body, or (2) the tumor may grow by infiltration, rows and masses of cells extending from the tumor into the spaces of the tissue about it. The tumor cells growing out in this way become separated from the mass and form independent centres of growth which by enlargement again join with the main tumor. A tumor growing by expansion shows a definite line of demarkation separating it from the surrounding tissue, but in the infiltrative growth, the line between the tumor and the normal tissue is not sharply defined and is often absent.

**TISSUE CHANGES.** The tissue in contact with the tumor shows various changes. In part it is merely pushed aside, the connective tissue becoming condensed from pressure; again the cells may become deformed and atrophied, and there may be necrosis from compression of blood vessels or because of the greater avidity of the tumor cells for nutrition. In certain cases the tissue may disappear before it, the tumor cells seeming to produce by contact a definite zymotic histolysis. Around the metastatic tumors in the liver these two modes of action are strikingly shown. There may be changes similar to the changes around foreign bodies, the formation of a granulation tissue with foreign body giant cells which show a marked phagocytosis for the cells of the tumors. Lymphoid cells in enormous numbers, and even diffuse lymphoid tissue with germinal centres, may be found at the edge of the tumor and extending into it. Polynuclear leucocytes are not present in any considerable numbers around or within the tumor save in those cases in which there is ulceration of the surface with infection. Necrotic tissue within the tumor may or may not exert a positive

chemotaxis for the leucocytes. Where surface ulceration takes place, a granulation tissue may be produced by the stroma and the tumor growth extends into this; but in other cases the base of the ulcer is formed by the tumor tissue with a line of necrosis on its surface.

**NUMBER.** Usually, tumors are single, but there may be multiple tumors of the same character arising from a single tissue. There is a marked tendency for the development of such tumors from the connective tissue sheaths of the nerves, appearing either on the nerve trunks or on the small nerves of the subcutaneous tissue. They often appear to develop simultaneously and to grow at the same rate. In such cases the conditions which give rise to tumor growth are operative not at one, but at many places. More rarely, several tumors of a different character are found. Such cases are sufficiently frequent to show that the presence of a single tumor does not prevent the formation of others.

**METASTATIC OR SECONDARY TUMORS** of the same character as the primary tumor may develop in other parts of the body. They represent an extension of the primary tumor not by continuity but by the conveyance of cells or tumor tissue to other places by means of the blood or lymphatics. The tissue around the tumor may be sown with such metastases or they may occur in more remote parts. These metastases are not determined by the accident of cell lodgment merely. The cells must find conditions favorable for growth; for example, the metastases may be confined to certain organs as the bone marrow or lymph nodes, even when we must assume that they have been carried to other places also. The development of metastases may take place at a comparatively late period of tumor growth, in cases where the physical conditions for their formation were present from the beginning. The metastatic tumors may show a much greater rapidity of growth than the primary and may occur in great numbers in every part of the body. They often show considerable differences in character as compared with the primary growth. The tumor cells find their way into the blood chiefly by means of penetration of the tumor into the lumina of vessels. Metastases within the blood vessels forming tumor thrombi are not uncommon and give origin to new (embolic) metastases. In a case of melanotic sarcoma observed by the author, with innumerable metastases, the tumor cells in the blood were so numerous as to be



evident on microscopic examination of a blood spread. Metastases within the blood may occur, the tumor cells growing in the blood as in any other tissue. Leukæmia should be regarded as a tumor of the blood forming organs with metastasis in the blood itself. Metastases by blood convection are more common in the lungs and in the liver than in any other organs. Metastases by lymphatic stream are caused by the entrance of tumor cells into the lymph spaces and lymphatics of the adjoining tissue thus appearing in those lymph nodes which receive the lymphatics from the region of the tumor. The cells are carried into the sinuses of the node and in these the metastatic growth usually begins. The nodes may prove a temporary dam to the extension, but with the continued tumor growth into the nodes there may be further extension by means of the efferent lymphatics. The tumor may grow for long distances within the lymphatic vessels. The thoracic duct may be filled with the tumor, or there may be a network of tumor growth filling the lymphatics of a region as those of the visceral pleura. The metastases by both blood and lymph vessels may occur in places opposed to the direction of the flow. This may be due to gravity, or to temporary slowness or cessation or even reversal of the current. The same conditions are seen with other forms of emboli. There are no hard and fast rules governing either the occurrence or situation of metastases. They are more apt to occur the more cellular and rapidly growing is the primary tumor, and the looser the relation between the cells and the intercellular substance. Metastases may also be due to the implantation of cells or portions of tumor over a surface which the primary tumor attacks as in the peritoneum or pleura. In the case of such metastases in the peritoneum, their situation, influenced by gravity, is more frequent in the pelvis than in other locations.

A tumor is a local disease. The growing tissue of the tumor, wherever found, is the disease, and it is evident that if all this material were removed the disease would be cured. This end is sought by surgical interference, but notwithstanding seemingly thorough removal of the growth, it often recurs at the site of operation, and even after an interval of months or years. There are many reasons for this. It is impossible to say just how far the growth extends into the neighboring tissues; the situation of the tumor may be such that an extended removal of the tissue about

it, which possibly contains the tumor cells, is impossible; cells from the tumor may be separated in the course of the operation and become included in the cicatrix; or the apparently recurring tumor may be a tumor of new origin not connected at all with the first. It is evident that the younger the tumor the less involvement there is of the surrounding tissue, and the more successful is the operation. It is also evident that a tumor growing by expansion can be more successfully removed than if the growth be infiltrating.

A tumor usually has the characteristics of the tissue from which it arises and the histological examination of the tumor may determine the tissue of origin. A tumor arising in a tissue, for example, the connective tissue, may approach in character closer to the embryonic than the adult type of this tissue.

In other cases, the tumor differs totally from the tissue of its apparent origin. In the situations where this occurs, misplaced tissues which in some cases have developed into the type of the normal adult tissue, and in others remain undeveloped, are not infrequently found, and tumors in certain instances undoubtedly arise from such embryonic remains. Adrenal tissue is not infrequently found either on the surface of the kidney or enclosed within it. Tumors showing the characteristics of adrenal tissue are found in the same relation with the kidney. Epithelial tumors may be found in the neck far removed from any epithelial structure and undoubtedly arise from remains of the epithelium of the branchial arches.

**DEGENERATION.** The cells of tumors may show the same types of degeneration which are seen in other pathological conditions. Fat is very commonly found in the cells, but, in the absence of other changes, it is not to be regarded as evidence of degeneration. The same is to be said with regard to glycogen and to the various hyalin masses seen within the cells. In cases of general amyloid infiltration, this may be seen in the tumor also. The cells in the interior of epithelial tumors with abundant stroma may show atrophy in various degrees due to deprivation of blood supply and may even disappear. The most common pathological condition, however, is necrosis. This may affect single cells or groups of cells or masses of tissue. The necrotic areas may be infiltrated by leucocytes, or these may be absent and no reaction whatever be seen in the surrounding tissue. The necrotic cells may form a

mass of granular detritis in which lime salts may be deposited, or they may undergo histolysis and be removed by absorption. We do not see the definite tissue reactions which are associated with repair and regeneration. Necrosis may be especially marked in rapidly growing tumors; death and absorption in the centre may almost keep pace with the rapid growth of the periphery. The most common cause of necrosis in tumors is disturbance of the circulation by compression of the thin-walled vessels, but extensive necroses which we are not able to attribute to this are sometimes seen.

**CELL CHARACTER AND FUNCTION.** The cells of a tumor repeat to a greater or less degree the morphology and arrangement of the cells of the tissue from which the tumor arises. Thus, in a tumor arising from a surface covered with cylindrical epithelium, the cells are generally cylindrical in shape and arranged in contact with each other along the long axis. The cells of a tumor of the adrenal gland show the characteristics of the cells of the gland. They may show some of the functions of the tissue, but this relationship is less evident than is the morphological. In tumors arising from the connective tissue, the intercellular substances are produced; in those arising from nonstriated muscle, myoglia fibrils are formed; and in those arising from neuroglia, the characteristic glia fibrils are formed; the bone tumors produce bone, and the cartilaginous tumors, cartilage. In tumors which arise from the surface epithelium, the cells show the same differentiation ending in the formation of keratin as the normal cells of the surface. In tumors of the adrenal glands, epinephrin is formed; in tumors of the thyroid, iodothyrein; in some of the adenomata of the liver, bile may be found in the cells; in tumors arising from the hypophysis and the pineal gland, changes are found in the body indicating the action of substances produced in these organs. The cells may produce large quantities of mucin, and this may appear also in the intercellular substance. Function is, however, always subordinate to growth; the energy of growth controls. Of the production of substances other than those of definite chemical composition or whose presence can be recognized by specific action, we have little knowledge. The chemical investigation of tumors has thrown little or no light on the subject, and what study has been made on the metabolism of individuals with tumors has also been without definite results.

Histolytic and hæmolytic ferments have been found in tumors, and in the early stages of carcinoma hæmolytic agents have been described in the blood. Evidence for the production of specific injurious substances in tumors is found in the condition of *cachexia*, a state of general malnutrition and anæmia, which is often seen in the late stages of the malignant tumors. There are many conditions accompanying such tumors which may bring about cachexia without the necessity for the supposition of specific activity of the tumor cells, as, for example, superficial ulceration and bacterial invasion, the closure of important canals, the destruction of organs, the absorption of necrotic products, pain and sleeplessness. This cachexia need not appear, and may be absent when all the conditions favoring it seem to be present. The tumor cells like other living cells receive from their environment the forces on which their activity depends and give off the products of metabolism. What these are, whether there is any common product associated with the excessive growth activity or whether every tumor differs in this regard, we do not know. The absence of evidence of the presence of such abnormal substances is no proof that they are not present. The organism may have adapted itself to the presence of such substances or they may be destroyed as they are formed. The autopsy findings in deaths from tumors have not thrown any light on this question. Terminal infection is common, the changes in the organs are in no sense characteristic and admit of ready explanation by the accessory conditions present at the time of death.

**RELATION TO ENVIRONMENT.** The tumor cell is not indifferent to the environment which the host offers. The variations in the activity of growth and formation of metastases, the unaccountable necrosis which may take place and, in certain cases, the disappearance of the tumor, all show this to be true. The relation of certain tumors to the age of the individual is another instance. The very common myomata of the uterus most usually appear during the period of sexual activity, and growth of such tumors may either cease or very greatly diminish when the period of sexual activity is past. Tumors of the mammary gland often show an excessive growth during pregnancy thus showing that the tumor cells also are influenced by the agents which induce the glandular activity of the organ. There must be an adaptation of the tumor to the individual which

leads to the symbiosis of tumor with host. In the tumors of animals it has been shown that the adaptation extends to the species, but never beyond this. In man the adaptation is individual, all attempts which have been made to transplant human tumors in animals and in other individuals having been unsuccessful. The metastases show, however, that there is more than a local adaptation, and successful implantation has been made of the tumor tissue into a remote part of the individual who bears the tumor.

**INFECTION.** Little is known as to the resistance of tumor tissue to infection. Pathogenic organisms are often found in tumors extending from surface ulceration or carried into them by the circulation. Enormous necroses may be associated with the presence of pyogenic bacteria. In one case observed by the author, nearly the whole mass of a large sarcoma of the thigh became necrotic after the injection of a virulent streptococcus into the tumor for therapeutic purposes. There have not been sufficient observations to determine whether the tissue of a tumor represents essentially new tissue or whether it shares in the characteristics which the other tissues have acquired, as in the case of general immunity. Numbers of observations on the experimental tumors of animals seem to show an extraordinary resistance of the cells. But it is not possible to determine the viability of the cells of human tumors by transplantation. So far as tissue study can tell us, the cells of human tumors show no special resistance to conditions producing death and disintegration in other tissues. The tissue of one tumor is not immune from metastases coming from a different tumor. I have several times found carcinoma metastases in a myoma of the uterus. Nor does an infectious disease confer immunity against tumor formation. The supposed antagonism between tuberculosis and carcinoma is due merely to the difference in the age period when these two diseases are most common.

**INHERITANCE.** Little is known with regard to inheritance in tumors. Studies on the tumors of mice show a greater susceptibility to tumor formation in the offspring of mice with spontaneous tumors. Some studies carried out on human families seem to show some positive influence on the descendants, but in the frequency of tumors such statistical evidence is of little value. The question has much bearing on the origin of tumors. If the tumor be merely an acquired condition due entirely to the action of causes extraneous

to the organism, there would be no hereditary influence; if, on the other hand, there is a special congenital predisposition of the tissues, whether in the cells themselves or in the fluids, arising as a variation, and associated with or underlying the tumor formation, we should expect an hereditary influence. The question is one which should be and can be determined.

**FREQUENCY.** The question as to whether tumors are increasing is equally difficult of solution. Vital statistics in every country seem to show an increase. The statistics of Massachusetts show between 1855 and 1905 an increase of 400 per cent. There are many factors, such as the increasing duration of life, the increasing certainty of diagnosis, the variation in the reliability of vital statistics, the movement of the population, etc., which are all difficult to estimate, and which must be considered in such statistics. The same may be said of the evidence for the greater frequency of tumors in general or of certain tumors, in different countries and localities. The opinion generally prevails that tumors are more numerous in highly civilized than in uncivilized peoples, but among the uncivilized no reliable method exists for determining frequency.

No age is immune from tumors. They may be present at birth or their development may begin shortly afterwards. From five to twenty is the most immune age, that from forty-five to sixty-five the most susceptible to the malignant tumors. Certain types of tumors predominate at different ages. The connective tissue tumors tend to appear at an earlier age than those arising from the epithelium.

**ÆTIOLOGY.** We know nothing as to the ætiology of tumors. Any cause must apply to all tumors, for the character of growth is common to all, just as there are common conditions in infections. No sufficient evidence has been brought forward to show that they are due to parasitic organisms. Various forms of bacteria and other organisms have been found in tumors, but with no constancy; and no tumors have been produced by inoculating with parasites. All the various sorts of cell inclusions which have been considered as protozoal parasites of unknown character have been shown not to be such. Support for the parasitic theory is found in the fact that parasites can excite proliferation of tissue and produce growths, but such growths, though they show some similarity to tumors, lack the distinguishing characteristics. No parasite has even been

found which can so alter the cells that the stimulus to growth given by the presence of the parasite will in the absence of the parasite be transmitted to the descendants of the cells. The parasitic theory would be difficult of application in the case of the congenital tumors. The theory, however, though at present lacking ground for belief, should not be dismissed as an impossible one.

Trauma as a direct cause of tumors, so changing the cells that they at once take on the characteristics of tumor cells, can be dismissed. There is too little ground for its support.

There are, however, a number of conditions which, though not immediately operative, may so alter the tissues as to make them susceptible to the action of another factor. Trauma, or injury of tissue, may be considered in this regard. There is an undoubted relation between tissue injury and tumors. Injurious agents which are continuous and slow in their action, and which produce continuous injury with equally continuous regenerative growth, are most effective in this respect. Tissues become separated in this way from their normal relations with one another. *Metaplasia* of tissue often takes place and there is a tendency for tumor development in such metaplasia. The tumor at the site of the injury may appear after years have elapsed. In certain cases the injurious agents seem to have a specific relation to tumor formation, as injuries by Roentgen rays, by the chemical injuries of coal products as shown by chimney sweepers' carcinoma of the scrotum, by the epithelial tumors of the skin and bladder in aniline workers. Parasites, such as the *Bilharzia Hæmatobium*, may produce changes in tissue which afterwards become the seat of tumors.

The germinal theory prominently associated with the name of Cohnheim must be considered in this respect. This is not a causal theory, the cause being the agency which produces the peculiar character of growth constituting the tumor. The theory of Cohnheim refers the origin of all tumors to remains of embryonic tissue, or to tissue which in the course of development has become misplaced. There is much in favor of this. There is a frequent — too frequent to be chance — combination between malformations of various sorts and tumors. The peculiar congenital *rhabdomyoma* of the heart is probably constantly associated with malformations of the central nervous system. Tumors frequently arise in places where there are complicated processes of development, as in the

regions of the embryonic fissures, and where two sorts of embryonic tissue join. They often develop from accessory organs as those related to the mamma, the adrenal gland, the pancreas, the thyroid and parathyroid. An excessive or misplaced tissue germ usually becomes either lost by gradual atrophy or it becomes differentiated simultaneously with the normal tissue into an accessory organ, or the differentiation may be so late that it forms a cyst as the dermoid cysts. There is really no close analogy between tumor cells and embryonic cells. Both show rapidity of growth, but the embryo cell growth proceeds to differentiation. Ribbert carried the theory of Cohnheim much further, assuming an origin for tumors, not only in such misplaced embryonic tissue, but in cells and tissue which, in consequence of trauma, or continued or long-standing inflammation, had become separated from their organic relations. All sorts of experiments have been made by design and accident in which cells and tissues have been separated from their normal relations; but a tumor has never been produced, nor has a tumor by any other procedure been produced experimentally. It is not impossible that two conditions are essential to tumor formation, a tissue capable of growth, and an agency acting on this which causes growth.

CLASSIFICATION. Some clinical purpose may be served by a division of tumors into those which are *benign* and those which are *malignant*. Such a division of tumors has very decided limitations. Strictly speaking, there are no benign tumors. The situation is of great importance. A slow-growing tumor without infiltration and without producing metastases may cause serious damage by the pressure which it exerts on important organs; for example, a slow-growing fibrous tumor of the dura. Apart from malignancy due to situation, the criteria are rapid growth, infiltration of surrounding tissue and formation of metastases. The results of microscopic examination are not always conclusive in determining malignancy.

Classification of objects always serves a useful purpose. It facilitates study and comprehension if the objects can be arranged into groups, each group including a number of factors common to all its members. So great is the diversity of structure in tumors, so uncertain in many cases is the histogenesis, that a classification based, as is the classification of the normal tissues, on structure



and histogenesis presents great difficulties. Nearly every one who has written on tumors gives a classification differing in various ways; but in any classification, individual tumors which cannot be placed will be found. A definition of tumors cannot be made on structure alone, but the character of growth must enter into it. If the ætiological factors were known, there would be some common and certain point from which to start. The anatomical classification of the lesions of tuberculosis was utterly confused until the discovery of the bacillus gave the possibility of a classification based on a common ætiology. Various names of tumors, which usage has so fixed that they cannot be rejected, have come down to us from the past. The name "*carcinoma*" or "*cancer*," which was given to certain tumors because of the fancied resemblance of the dilated overlying subcutaneous veins to the outstretched legs of a crab, is used loosely to signify a malignant tumor of any character and specifically as a name for a malignant tumor derived from epithelium. The name "*sarcoma*," now generally used to signify a tumor originating in the connective tissue, but differing in various ways from the normal type of this tissue, was originally used to designate a tumor of a fleshy character. Virchow, with his great experience and wide comprehension, divided all tumors into three groups. The *histoid group*, embracing those tumors composed in whole or in great part of a single tissue similar in character to some one of the normal tissues; the *organoid group*, into whose structure two or more tissues, arranged in a certain order, entered; the *teratoid group*, into whose structure systems of tissue entered and which formed the connecting link between tumors and monstrosities. The classification must be based so far as possible on similarity of structure to the normal tissues, and the histogenesis, as far as this can be ascertained, should also enter into it. Histogenesis, even of normal tissue, is not on an absolutely certain basis and still less certain is it in the case of tumors. The analogy of tumor structure with that of normal tissue is found in the character and arrangement of the cells and the formation and character of the intercellular substances.

The following classification of tumors based on character and embryonic origin of the tissue is the simplest and generally adopted.

Tumors of the Connective Tissue Class.	{	Fibroma
		Myxoma
		Chondroma
		Osteoma
		Lipoma
		Myoma {
		Leiomyoma
		Rhabdomyoma
		Melanoma
		Angioma
	{	Sarcoma — this name, used partly alone, partly as an appendage to other names, as fibro-sarcoma, myxo-sarcoma, etc., designates tumors of the connective tissue group which vary widely from the normal type of these tissues, in relation of cells and intercellular substance, and in rapidity of growth.
Tumors of Epithelium	{	Papilloma
		Adenoma
		Carcinoma
		Chorioepithelioma
		Hypernephroma
Tumors of the Nervous Tissues	{	Neuroma
		Glioma
Tumors of the Blood Tissues	{	Lymphoma
		Chloroma
		Myeloma
		Leucocytoma
Tumors of Endothelium	{	Endothelioma
Tumors of Embryonic Character of Tissue	{	Embryoma

TERATOMATA are tumors of embryonic tissues, but which have to a greater or less degree developed in a normal manner and which show a coördination of structure.

It cannot be pretended that such a classification as this is scientific, it is merely pragmatic.

Tumors have been found in most of the mammalia both those in domestication and in the feral state. They have also been found in some of the cold-blooded vertebrates. The tumors found vary in structure and in character of growth. They have so much in common with tumors of man that they fall into the nomenclature of human tumors. There seems to be some relation between the tumor character and genus; thus, in fowls tumors of the lymphoid type are most common. Metastases occur and chiefly by the blood, but not with the frequency which is seen in human tumors. The presence of one tumor confers no immunity from the occurrence of other spontaneous tumors. They show a decided difference from the tumors in man in that the adaptation between tumor and host tissue extends to the species. But it does not go beyond this. Even within the species the adaptation may be limited to certain strains. These tumors may be transplanted from one individual of a species to another by placing beneath the skin or in other suitable situations cells or portions of the tumor tissue which grow in the new situation. The process is comparable not to the inoculation of parasites, but to the grafting of plant tissue. Tumors of a simple structure corresponding with Virchow's histoid group are less easily transplanted; their adaptation may be confined to the bearer. The virulence of the tumors, i.e., their capacity for growth and for overcoming the resistance of the tissues, may be increased by constant transplantation. The resistance of the animal to the implantation may by various procedures be increased up to the production of complete immunity. After spontaneous recovery from a tumor immunity is established and may be passively transferred by means of the serum of the resistant animal to another. Immunity may be given by a previous inoculation with another nonvirulent tumor, it may also be given by a previous inoculation of the animal with foetal and even with adult tissue. The immunity is not specific. Immunity against one sort of tumor will protect against a tumor of different character. In the course of transplantation a tumor may change its character, a carcinoma, for instance, changing into a sarcoma. Most prominently there has been shown that in tumor growth there must be an adaptation between tumor tissue and host. The possibility of adaptation varies and may be experimentally increased or diminished.

## CYSTS

These have so much relationship to tumors that the general subject may be considered here while the special forms will be considered in the special pathology of the organs. A cyst is a collection of fluid or semifluid material in a circumscribed cavity in the tissues. It is evident that cysts may arise in various ways and may be divided into:

**RETENTION CYSTS** represent a collection of fluid in a gland or a duct or any epithelial-lined structure due to closure of ducts and the retention of the products of secretion. Such products may be so changed as to offer but little similarity to the normal secretion. There is a growth of epithelium which keeps pace with the enlarging cavity and often exceeds it. The wall is thickened by a reactive growth of connective tissue, the surface may be round and smooth or irregular with projections into the surrounding tissue, as, for example, in cysts of the pancreas.

**EXTRAVASATION CYSTS** are due to hæmorrhage in the tissue. After the absorption of the blood a cavity filled with tissue fluid may result due to the inability of the walls to collapse as in the case of the brain. Example, apoplectic cyst.

**EXUDATION AND TRANSUDATION CYSTS** are due to the accumulation in a cavity of an exudation or an increased transudation. Example, hydrocele.

**CYSTS FROM SOFTENING AND DISINTEGRATION OF TISSUE** may arise in a tumor, or in any organ of the body, as in the brain. After cerebral softening cysts always appear.

**CONGENITAL CYSTS** may be present at birth or develop afterwards. They are due to disturbances in development in consequence of which tissues may be isolated and enclosed in a different tissue, and in consequence of cellular activity a secretion is formed and included in the tissue. Example, dermoid cyst of the skin. Or there is imperfect formation of canals. Example, congenital cystic kidney. Or there may be persistence of embryonic canals or tissues which should have disappeared in development. Example, cysts of neck arising from remains of branchial arches,

cysts of vagina formed by remains of Mullers ducts. There is no sharp line separating the cysts from the tumors.

**CYSTIC TUMORS** are tumors in which the presence of fluid in closed spaces is a prominent characteristic. The fluid is due to the activity of the tumor cells. Example, cystic tumor of ovary.

## CONNECTIVE TISSUE TUMORS

**FIBROMA**, a tumor originating in the connective tissue and conforming in structure to the type of this tissue. The tumor is composed of cells, intercellular substances in fibrillar form and vessels. Such tumors may form in any part of the body, but they are most common in the subcutaneous connective tissue and in the corium. They may be perfectly circumscribed or closely connected with the surrounding tissue. Three forms of fibroma are recognized, the *fibroma molle*, *fibroma durum* and *keloid*. The fibroma molle is a soft elastic tumor composed of delicate interlacing fibrils, a varying amount of tissue fluid, sometimes so abundant as to give rise to the name oedematous fibroma, the cells generally of spindle shape lying in close relation to the fibrils. The blood vessels are abundant and there is frequently a condensation of the tissue about them. The fibroma durum is a hard tumor, on section white and refractile, with interlacing connective tissue bands. The intercellular substance is composed of bands of coarse fibres which apparently are formed by the fusion of single fibrills, the cells are small, the nuclei elongated, the cytoplasm not evident, and they lie either within or on the outside of the bands of fibres. Cross sections of the bands resemble sections of tendon. The vessels are not numerous. The keloid is a hard, dense, white tumor often arising from scars and in structure closely resembling scar tissue. It is composed of closely interwoven bands of large, dense fibres with few and small cells lying chiefly in the interstices. The vessels are few. These tumors are more common in negroes, particularly in those living in the tropics. A special form of fibroma arises from the connective tissue of nerves. These tumors usually are multiple, often appear simultaneously, and may affect either the larger nerves or the small nerves in the subcutaneous tissue or both. The tumor is of importance chiefly in that it serves as the type of the systemic tumors. Thousands of small or large, often pendulous, soft tumors may appear in the subcutaneous tissue. Along the nerves the tumors, often in great numbers, form hard, round or spindle-shaped, circumscribed masses, and where the

nerves pursue a tortuous course, irregular, convoluted, interlaced masses (*plexiform neuroma*). The nerve fibres, which take no part in the tumor growth, may pass over the surface or in bundles through the interior.

The fibroma has no relation to age and does not tend to recur after removal save in those cases where the limits of the tumor are not sharp or where, from the situation, complete removal is difficult. It does not produce metastases. There is every gradation between the fibromata and the sarcomata in relative numbers of cells, and in the relations of the cells to the intercellular substances. To such intermediate tumors the name *fibrosarcoma* is given.

The close relation between the normal epithelium and connective tissue may be repeated in tumors. The fibroma of the skin may develop in the subcutaneous tissue or in the lower corium or in the papillary layer. In the latter case the papillæ grow with the tumor and may become elongated, enlarged and give off numerous branches. The name **PAPILLOMA** is given to the tumors in which the growth of the papillæ is the most marked characteristic. There is an accompanying new formation of epithelium which may greatly exceed the normal. It is possible to divide the fibro-epithelial tumors into two groups depending upon the tissue which has the dominating place in growth. The subject is also considered under adenoma. Fibromata developing beneath mucous surfaces form pendulous projections called polypi. The fibrous tissue usually is soft and oedematous and may contain much mucin giving to the growth a gelatinous translucent character. The surface epithelium rarely shows an excessive growth, but when glands are present there may be much new formation of glandular tissue. In certain cases it is difficult to say whether the connective tissue or the epithelial growth is the dominant factor. Such tumors are best classed under the name fibro-epithelial tumors, and there is no morphological distinction between them and similar combined connective tissue and epithelial growth due to chronic irritation often of infectious character.

Very similar growths are found in glandular organs, particularly in the mamma. A growth of the connective tissue here will extend into the ducts and acini of the gland. These become greatly dilated and filled with a complicated branching mass of papillæ appearing on section as isolated masses of fibrous tissue covered

with epithelium. The epithelial growth may be in excess and spaces corresponding to acini appear within it. These tumors usually are circumscribed and on section show numerous fissures corresponding to the dilated ducts. They are given the name "*intracanalicular fibroma*" or when the epithelial growth is excessive "*intracanalicular adeno-fibroma*."

**MYXOMA**; a tumor of the connective tissue type characterized by the presence of mucin in large amount in the intercellular substance. The normal type of this tissue is found in the umbilical cord. These tumors may form in the connective tissue in any part of the body, and may be of any size. They vary in consistency and have a transparent gelatinous appearance. On microscopic examination there is always a varying amount of fibrous intercellular substance and a clear structureless material which stains faintly with hematoxylin. The cells, which vary much in numbers in different tumors and in different parts of the same tumor, are spindle or stellate in form. The tumor is more malignant than the ordinary type of the fibroma. Blood vessels are relatively abundant and extensive hæmorrhages often occur. The myxoma has not a very definite place in the list of tumors. Mucin is found in all connective tissue and in varying amounts in all the connective tissue tumors. It may be increased in amount in tissues undergoing atrophy as in atrophy of fat. Myxomatous tissue occurs more often in tumors in combination with other types of tissue as fat, cartilage, bone, than in pure form. Its presence is recognized in the nomenclature in combination with other tumor names as myxofibroma, etc.

**LIPOMA**; a tumor composed of fat tissue. Most common in subcutaneous tissue, but may be found in the internal fat and rarely in places where fat is not normally present, as in the brain, spinal canal or in the interior of organs. In these latter places it undoubtedly arises from fat-forming tissue which was misplaced in the course of embryonic development. The tumors are smooth on the exterior, round or lobulated, and so loosely connected with the surrounding tissue that they may change their position by gravity and form new vascular connections. They are rather more yellow than the normal fat. Fibrillar connective tissue, always present, varies in amount being sometimes so abundant that the name fibrolipoma is used. The cells usually are larger than normal



fat cells and there seem to be centres of growth where the cells are small and the fat in small droplets in the cytoplasm. The pure lipomata may appear at any age, they have few vessels, grow slowly and constitute the type of benign tumors. The largest lipomata are those which appear as circumscribed tumor masses in the retro-peritoneal fat. A special form of lipoma, known as *xanthoma*, occurs in the skin, especially on the eyelids, in the form of small, circumscribed, flat, yellowish-brown tumors. Microscopically, the cells contain yellow pigment and fat in the form of small droplets.

Fat tissue has great power of growth and there is no sharp line of demarkation between the lipomata and the diffuse formation of fat which may affect all the fat organs or be confined to the fat tissues of one part of the body, as in *adiposis dolorosa* and similar conditions.

**CHONDROMA**; a tumor composed of cartilagenous tissue. They most commonly are found connected with the skeleton and arise from the perichondrial or periosteal tissue. They frequently are multiple, and form hard, knobby, irregular masses. They may arise also in the soft parts. They are gray in color, pearly and translucent. They are extremely irregular in structure and the normal types of adult cartilage are rarely found. The intercellular substance, usually hyalin, contains chondrin. The cells may lie in definite capsules, but usually are devoid of these, and in number and form vary greatly, being round, spindle or stellate. Often large areas of homogeneous intercellular substance are found containing no cells, but filled with spaces formerly occupied by them. Extensive necroses are common and the necrotic tissue becomes infiltrated with lime salts forming large irregular masses. In other cases bone is formed, either true bone or an imperfect osteoid tissue. Cysts filled with glairy mucoid fluid due to softening of the tumor tissue are not uncommon. The skin over the tumor may ulcerate from pressure and an ulcer with a cartilaginous base be formed. Such ulcers, lacking the protection of granulation tissue, easily become the atrium of infection and extensive necrosis of the tumor with abscess formation may result. Cartilage is much more frequently found in combination with other tissues than alone. It seems easily to pass into myxomatous tissue; there may be much fibrous tissue and this may be of sarcomatous type. Combined

names such as myxo-chondroma, fibro-chondroma, chondro-sarcoma are given to signify such combinations. The chondromata, especially the mixed forms, are not benign tumors. They may form immense tumors, often of rapid growth, infiltrating the surrounding tissue and producing metastases by the blood stream, the vessels often being penetrated by the tumor growth.

**OSTEOMA**; a tumor formed of bone. The normal type of bone is repeated in the tumors, but there usually is some irregularity in the lamellæ and in the corpuscles. These tumors usually are connected with bone, the tissue of the normal bone passing directly into the tumor; or they may be formed from seemingly independent centres of growth with a definite line of separation between the bone and the tumor. In one variety of osteoma, known from its hardness as the ivory osteoma, the bone is exceedingly dense, contains few vessels, relatively few bone corpuscles and takes a high polish similar to ivory. The spongy osteoma is the opposite of this. The osteoma grows slowly, does not infiltrate and does not form metastases. No sharp line can be drawn between these tumors and the various formations of bone which take place in the body due to a variety of conditions. Bone formation also occurs in a number of other tumors especially in the chondromata and in sarcomata arising from the periosteum. The true osteomata are rare tumors and have no relation with age.

**LEIOMYOMA**; a tumor formed of non-striated muscle tissue and arising from this. The long spindle-shaped cells with thin rod-like nuclei and the myoglia fibrils characteristic of this tissue are repeated in the tumor. The fibres are arranged in interlacing bands giving to the cut surface a reticulated appearance. The tumors usually are smooth on the surface, easily separated from the surrounding tissue which often forms a capsule around the tumor, and do not produce metastases. The great frequency of these tumors in the uterus makes the myoma one of the most common tumor forms. In the uterus they often are multiple and may attain a great size. Necrosis and hyalin degeneration is common. Cysts may be formed from the liquefaction and the absorption of the degenerated areas. Not infrequently the entire tumor may become calcified following necrosis, and there often is a considerable admixture of fibrous tissue. In certain of these tumors, often described as sarcoma of the uterus and which represent a malignant

type of the myoma, the growth is active, the formation of myoglia fibrils greatly diminished and the cells appear as short spindles with oval nuclei rich in chromatin. The sarcoma-like growth may appear in one part of the tumor, the remainder having the ordinary type. These tumors grow rapidly, are infiltrating and produce metastases. It is obvious that such tumors bear the same relation to the ordinary myoma that the sarcoma bears to the fibroma.

**HÆMANGIOMA**; a tumor composed largely of blood vessels, these not merely serving the purpose of nutrition, but forming an integral part of the tumor. The vessels are supported by fibrous tissue. There is no differentiation of the vessels in the tumor, nor are their walls distinct from the supporting tissue. Two forms of these tumors are recognized, the simple and the cavernous; in the latter, most common in the liver, the vessels form large communicating spaces. The simple hæmangiomata may form large rapidly growing infiltrating tumors. The congenital vascular nævi are separated from the hæmangiomata in that they represent chiefly a dilatation and elongation of the normal vessels of the part.

**LYMPHANGIOMA**; a tumor representing the same sort of formation from the lymphatic vessels. It may appear in the form of large communicating cystic spaces filled with lymph. I have seen two such tumors, one in the spleen and one in the subcutaneous tissue of the arm. In the other form small communicating spaces are found usually in the midst of lymphoid tissue. It is uncertain as to what extent dilatation of pre-existing vessels enters into their formation. There is a congenital form found in the skin similar in character to the vascular nævi and like these due chiefly to dilatation of pre-existing vessels. The most common types of these tumors are represented in macroglossia and macrocheilia.

**ENDOTHELIOMA**; a great confusion exists in regard to this tumor. In both the hæm- and the lymph angioma the growth proceeds from the endothelial cells which form vessels, the vascular formation here being analogous to the new formation of vessels in granulation tissue. In the endothelial tumors the growth of the endothelium does not conform to the physiological type, but is excessive, the cells invading and growing into the tissue, often forming whorls or growing in long lines. Usually places can be found in the tumor where the endothelial growth is taking place within vessels containing blood or lymph. The cells lose their

character as flat lining cells and more closely resemble epithelium. These tumors may be of rapid growth, infiltrate the surrounding tissue and form metastases. Combinations between the angioma and the endothelioma are not infrequent. It is a question as to whether the tumors arising from the lining cells of the great body cavities should be placed with the epithelial or the endothelial tumors. Both the normal cells and the cells of tumors arising from them share many of the characteristics of both epithelium and endothelium. The endothelioma of the dura arising from cells histogenetically related to the peritoneum or pleura form an especial type of tumor. The cells are small, flat and usually arranged in connected masses lying in a connective tissue stroma. Often they form concentric whorls. Endothelial growth from the vessels seems also to enter into the tumor formation. The concentric whorls of cells may, after necrosis, become hyaline or calcified forming sand-like masses (psammoma).

SARCOMA, a tumor arising from the connective tissue, in structure departing from the normal type of this tissue in the abundance and character of cells and the relatively slight formation of intercellular substance. The tumors have been compared to the connective tissue of the embryo and to granulation tissue, but there is really little analogy either with embryonic or with inflammatory tissue. They may develop in the connective tissue in any part of the body and are most common in such tissue as the periosteum and connective tissue sheaths and fasciæ. The differentiation between the sarcoma and the epithelial tumors may be difficult. One of the most characteristic features of the tissue from which the sarcoma develops is the formation of intercellular fibrils. This is found to a greater or less extent in the sarcomata. In certain of the very rapidly growing sarcomata this characteristic may be lost and all of the energies of the cells take the direction of growth. In such cases masses of cells may be found, separated by an imperfect stroma which partly represents the old tissue into which the tumor has penetrated and is in part newly formed by the tumor cells. Fibrils from the stroma may penetrate between the cells at the periphery of the cell masses and the general relation between cell mass and stroma is much closer than in the epithelial tumors. Such tumors often are called alveolar sarcomata. The vessels, usually abundant, may be nothing more than mere fissures in the

tumor lined with endothelium. Hæmorrhage and necrosis are common. Metastases take place chiefly by the blood stream. The secondary nodules may grow with great rapidity and differ in structure from the primary tumor. The cells sometimes show a mantel-like arrangement along the vessels. Such tumors have been called peritheliomata or perithelial sarcomata, but there is no perithelium around the vessels from which such a specifically named tumor can develop. The sarcomata vary greatly in malignity. No tumor shows such rapidity of growth or tendency to produce metastases as do certain of the sarcomata. According to the character of the cells sarcomata are divided into:

**ROUND CELL SARCOMA.** The cells have a generally round shape, vary in size in different tumors, often are arranged in alveoli. The intercellular substance usually is small in amount and may form a reticulum around the cells.

**SPINDLE CELL SARCOMA.** The cells, of spindle shape, usually are closely compacted in interlacing bands in the interior of which are the blood vessels. A small amount of intercellular substance and usually bands of fibrous tissue enclosing the larger vessels are found.

**GIANT CELL SARCOMA.** Usually in combination with spindle cells, giant cells may be found in sarcomata. These vary in size, may be very numerous, and have no especial characteristics, are round, elongated and irregular in outline, with the nuclei distributed irregularly in the cytoplasm. Such cells may be found in sarcomata which develop in the soft tissue, but more usually are found in those developing from the bone, though there is little tendency to bone formation in the tumor. These tumors are slow in growth, and have no tendency to metastases. They may disappear spontaneously, and cysts may be formed from their degeneration.

Mixed cell sarcoma is often used to designate the tumors in which the cells are of an indeterminate character or a mixture of various forms. Sarcomata arising from bone or from the periosteum show two types dependent upon the character of the accompanying bone formation. In the osteo-sarcoma there is a varying amount of bone formed which approaches or repeats the normal type; in the osteoid sarcoma the calcification may be very imperfect or absent, the bone being represented by a hyaline, often reticular structure in which groups of cells lie.

**MELANOTIC SARCOMA.** These tumors, characterized by the formation of pigment, deserve a definite place in the classification of tumors. The pigment is melanin. It is formed, in varying amounts, by the tumor cells and varies in color from brown to intense black. In some cases it is present in such large amounts that it is excreted by the urine, giving this a characteristic color. The tumors arise either in the choroid of the eye or in the skin. In the latter place they often develop from the congenital pigmented *nævi* or moles which have much the same histological structure as the tumor. The cells vary in size and shape and tend to arrangement in more or less well-defined alveoli. Areas of the tumor may be entirely free from pigment. Metastases occur early, and are very numerous. The primary tumor may be quite insignificant in comparison with the metastases. The melanosarcoma is one of the most malignant of tumors.

**NEUROMA.** Tumor-like masses may arise from regeneration of the cut ends of the nerves in an amputation stump. In the neurofibromata the nerves take no part in the tumor formation. True neuromata are extremely rare and confined to congenital tumors often of a very malignant character, arising from the sympathetic system. These may contain cells of the ganglionic type and nerve fibres, or, in the midst of an indeterminate sarcoma-like tissue, clusters of small cells with sheaves of fibrils in connection with them are found. Closely allied to the neuromata is the neuroepithelioma, a congenital tumor of the retina. This tumor is composed of small cells often circularly arranged around spaces, forming rosettes. Around the space there is a more or less well-differentiated cuticular border through which pointed or blunt processes of the cells project, suggesting, and probably imperfectly representing, retinal rods and cones. The cells of these congenital neuromata are very similar to the early, undifferentiated nerve cells in the embryo.

**GLIOMA.** Tumors developing from the neuroglia show great variation in character. The cells of the neuroglia, a tissue of epiblastic origin, occur as the epithelial-like ependymal cells and, in association with intercellular fibrils, as the general supporting tissue of the central nervous system. The characteristic features of these tumors is the presence of neuroglia fibrils. Spaces lined with cells analogous to ependyma may be found. The

relation of cells to fibrils varies and the cells may, in type and arrangement, simulate a carcinoma. Hæmorrhage and necrosis are common. The growth, usually slow, may be very irregular. It seems to be influenced by the intracranial pressure and may increase rapidly after decompression operations. The term gliosarcoma has, without justification, been applied to the very cellular gliomata. Generally the gliomata are tumors of slow growth, not sharply circumscribed and do not produce metastases, being malignant from situation only. They develop rarely outside the central nervous system from embryonic displacements of neuroglia. A glioma developing from the neuroglia of the brain may project from the surface and, growing along the pia, simulate a tumor originating in this membrane.

**RHABDOMYOMA**, a tumor always of embryonic origin whether congenital or not, characterized by the presence of imperfect forms of striated muscle tissue. Two chief forms of this are seen: spindle cells, sometimes joined, with characteristic striation of the cytoplasm, and large, irregular vacuolated cells with the sarcous elements appearing as pairs or rows of dots. The typical embryonic hollow cylinders with exterior striation are not found. These tumors may appear in the heart or in some relation to the genito-urinary system. In the latter situation there is always an admixture of other sorts of tissue. The rhabdomyomata of the heart usually are accompanied by some form of malformation of the central nervous system.

## TUMORS OF THE BLOOD

The pathology of this system is complicated and difficult of clear comprehension. This is due in part to the fact that the embryonic condition persists in adult life. Regeneration takes place, not by multiplication of cells which have undergone a complete differentiation, but by growth of a persistent embryonic tissue, the cells becoming differentiated in the process of their development. The tissue has great power of growth, this being shown not only in the formation of new cells in the numerous foci of the tissue which normally are present, but by the fact that new foci easily arise. Under normal relations the undifferentiated cells remain at the foci of formation (bone marrow and lymph nodes), but in pathological conditions these undifferentiated cells also may pass into the circulation. The tumors have become confused with the hyperplasia of tissue, the result of reaction to injury, which may greatly resemble tumor formation and in which unusual cell forms appear. Bearing this in mind, we still can single out from the confusion of tissue changes and the equally confused nomenclature certain entities.

**LYMPHOMA**, a tumor of the lymphoid system formed of lymphoid cells, but without the tissue structure of the lymph node. It is uncertain whether or not multiplication ever takes place from the small cells which we are accustomed to think of as the representative cells of the lymphoid system. The cells which compose the main mass of the tumors conform closely in size and structure to the cell type as found in the germinal centres of the lymph nodes. The tumors may appear primarily in any part of the lymphoid system, the growth being characterized by periods of inactivity and periods of great rapidity of growth. At times the tumors seem to arise from a single focus with a rapid secondary involvement of other similar tissue; at others the tumor formation may appear as a system disease, similar to neuro-fibroma, in a number of foci simultaneously. Metastases are formed in great numbers by both the blood and the lymphatics and may appear in all the organs of the body. Hæmorrhages are very frequent in the metastases, less frequent in the primary tumors.



**MYELOMA**, a tumor arising in the bone marrow. It is impossible to say which one of the cell series in the marrow constitutes the mother cell. The cell outline is sharp, the cytoplasm dense without definite granulation, often strongly basophilic, in which case the cells somewhat resemble plasma cells, or it may be neutrophilic or even acidophilic. The nuclei are large, very distinct, and in most cases contain a large, definite, acidophilic nucleolus. The tumor is destructive in growth, and there is little or no accompanying periosteal bone formation. The growth varies at different periods, at times apparently ceasing, and the tumor may even retrogress in size, these periods being followed by very active growth. The tumors may be single or multiple. Metastases are infrequent, but may occur in the lymph nodes and elsewhere. Bence-Jones albumosuria has been found very generally in the urine in cases of myeloma.

**CHLOROMA**, a peculiar and rare tumor arising most usually in the bones of the face and orbit and characterized by the presence of green or greenish-yellow pigment which fades on exposure to the air. The cells are indefinite in character, resembling large lymphocytes.

**LEUKEMIA**. It is most convenient to consider this in connection with the tumors of the blood system. The name should be regarded as a clinical term to describe a condition in which large numbers of white cells are present in the blood. These may be so numerous that the blood becomes purplish or lilac in color. Two forms of leukemia are recognized: one, myelogenous leukemia, in which the excess of cells are of the myelocyte type; the other, lymphatic leukemia, in which the cells are of the lymphoid cell type. In many cases these types are not pure and the name mixed-cell leukemia is used. In all cases, but especially in the myelogenous leukemia, there is an enormous excess in the amount of blood. All the veins are dilated and the greatly increased weight of the organs (weights of liver and spleen up to 5000 grams each are not uncommon) is due mainly to the amount of blood contained in them. Neither hypertrophy nor dilatation of the heart accompanies the condition.

**LYMPHATIC LEUKEMIA**. In cases of lymphoma the tumor cells easily find access to the blood either directly or through the lymphatics. In autopsies on cases of lymphoma the cells often are

present in the vessels of internal organs in considerable numbers. It is possible that these cells, the conditions being unfavorable, are destroyed in the blood. The lymphatic leukemia represents those cases of lymphoma, in which, along with other metastases, there is metastasis in the blood. The extraneous tumor cells entering into the blood find conditions favorable not only for preservation, but for growth. The cell forms in the blood, especially in the more acute cases, may repeat those found in the tumors or there may be a further differentiation with the fully differentiated lymphoid cell chiefly represented. In the more chronic cases the metastases are less numerous, larger in size, and are especially marked in the spleen. This may be greatly enlarged and filled with grayish tumor masses. The cells in the blood are chiefly of the small differentiated type.

**MYELOGENOUS LEUKEMIA.** This is due to a tumor formation in the myelogenous tissue analogous to that taking place in the lymphoid tissue in lymphatic leukemia. The cell forms represented in the blood are premature or mature myelocytes. The fat in the marrow disappears and the marrow of all the bones is filled with an opaque, gray-red mass of soft tissue in which the medullary spicules of bone may be absent. The marrow in all of the bones is affected, so that the condition is to be regarded as a systemic tumor. Metastases of myelogenous tissue are found, but are not so definite as those in lymphoma. The myelogenous cells not only pass from the marrow into the blood, but multiply there, nuclear figures being found in the circulating cells. There are no cases of the tumor formation in the marrow without the metastases into the blood. There is no distinct name for this tumor formation. The name myeloma refers to a very different process in which there are no blood changes.

In both the lymphoid and the myelogenous forms of leukemia there may be an admixture of the cell types, but one type predominates. It is natural that there should be some admixture in cell proliferation in two systems so closely related as the myelogenous and lymphoid tissues. The bone marrow under normal conditions contains lymphoid cells and in lymphatic leukemia may be almost as fully involved in the tumor formation as it is in the myelogenous forms.

## EPITHELIAL TUMORS

The epithelial tissue in its power of growth, regeneration and function is the most active of all the tissues. With the exception of the nervous system the epithelium wherever found is in relation with surfaces which, except in the ductless glands, are in communication with the exterior. The various sorts of epithelium have great differentiation in function which to a great extent is expressed in their morphology. There is everywhere a close relation between epithelium and connective tissue, proliferating epithelium being accompanied by a new growth of blood vessels and a supporting stroma of connective tissue. This close relation is expressed in the fibro-epithelial tumors, in which it often is impossible to decide which of the two tissues predominates. The structural differentiation of the different epithelia is to a considerable extent preserved in the tumors. There are no epithelial tumors in which the cells in morphology and mode of growth show such complete absence of differentiation as is seen in certain of the sarcomata. The essential elements in the epithelial tumors are the epithelial cells. The stroma coming from the adjoining tissue is secondary. According to the relation of the cells and stroma the epithelial tumors can be divided into two great classes, the adenomata and the carcinomata.

**ADENOMA.** In the adenoma the cells have the same relation to the stroma as is found in normal glandular tissue; there are alveoli lined with epithelial cells separated from the connective tissue by a basement membrane. In the tumor this arrangement is preserved, the cells retaining their relations and pushing out the separating membrane before them. In certain glands, in addition to a *membrana propria*, there is an enveloping layer of smooth muscle fibres and this also enters into the structure of the adenoma. In the formation of the tumor the cells at some point of the wall of an epithelial-lined cavity begin to proliferate forming a small mass into which the blood vessels from the stroma grow. With the

continuation of the growth and with the formation of other centres of growth into which secondary papillæ project, most complicated structures arise. The cavity in which the growth started enlarges with the growth of the branching masses within it. In most adenomata both forms of growth are seen, but one or the other usually predominates. When the papillary form extends to such a surface as the peritoneum portions of the papillæ are easily broken off and form new attachments and new foci of growth. The cells lining the alveoli of an adenoma may not lose their secretory power and the accumulation of the secretion leads to the formation of cysts. The name adeno-cystoma or papilliferous adeno-cystoma applies to these conditions. It is obvious that there is no essential difference between any epithelial-lined cavities or canals and the alveoli of a gland; in such cavities and canals papillary epithelial growths may be formed. The character of the papillæ may vary, in one case being extremely long and thin with many branches, in others being shorter and broader. The character of the papillary growth seems to depend upon the character of the epithelium or possibly upon the contents of the cavity. In certain places, as in the bladder, such papillary tumors are malignant. In other cases true carcinomata develop at the base of the tumor, the epithelium growing into the surrounding tissue.

CARCINOMA is an epithelial tumor in which the character of the epithelial growth is atypical and the resulting tumor structure has no analogy with normal epithelial organs. The essential characteristic of the carcinoma is that the cells have the capacity of invading the tissue growing out in it and penetrating the tissue spaces and lymphatics. They do not retain their normal relations with each other nor with the stroma. They often, to a great extent, retain the morphological characteristics of the epithelium from which the growth arises, but may be very dissimilar and rarely show any indication of function. Usually they are larger than the corresponding normal cells, have an abundant compact cytoplasm, and one or more large vesicular nuclei rich in chromatin. It is natural that such an epithelial tumor, with an unlimited power of growth of the constituent cells, and capacity for invading the adjoining tissues, should form the prototype of a malignant tumor. The carcinoma extends locally by infiltration, secondary nodules being formed in the vicinity by ingrowth

of cells or their conveyance along the lymph spaces. Metastases arise from cells conveyed to other parts by the blood or lymph circulation and there is marked tendency to recurrence after removal. The epithelial cells of a carcinoma in the beginning form a single connected mass penetrating the tissue. Single cells may become detached and form new centres of growth. Section of the tumor always shows masses of epithelium surrounded by connective tissue and blood vessels. The separation between the stroma and epithelial masses is sharp. The shape and direction of the epithelial masses depend to some extent upon the course of the lymphatics. An epidermoid carcinoma near the surface shows perpendicular extensions, but lower down they are more horizontal. The size of the alveoli varies. They may be very large, or composed of but a single line of epithelial cells. The growth of the tumor is most active in the periphery. The active growth of the cells in the periphery may interfere with the nutrition of the centre of the tumor by compression of the vessels so that active peripheral growth may be accompanied by atrophy, necrosis and contraction of the centre. Nuclear figures are abundant and often show atypical forms. Ulceration in carcinoma is common. When the growth reaches the surface the covering epithelium is deprived of its nutrition, undergoes necrosis sometimes with preceding vesicle formation and is cast off. In such ulcers, there may be formation of granulation tissue which is invaded secondarily by the epithelial cell masses. The tumors may vary greatly in character, and such variations have received different names. The ordinary type, showing the usual relation between alveoli and stroma, is called carcinoma simplex. Scirrhus is used to describe those forms in which the stroma is abundant, firm, and the whole tumor shows evidences of contraction. In medullary carcinoma the alveoli are relatively large and the stroma small in amount. The medullary and scirrhus types may be present in the same tumor. Ulceration is always a marked feature in carcinomata of the alimentary canal. The general type of such tumors is a central, deep, more or less clean ulcer surrounded by an elevated wall of growing tumor. The growth is often encircling because of extension along the lymphatics. Stenosis of the canal results, due both to contraction of the stroma and to the projecting tumor masses. Transition forms between the adenoma and carcinoma are not infre-

quent. In a tumor starting as an adenoma, the typical epithelial growth may become changed into the atypical growth of the carcinoma. In the same way in the carcinoma, a tendency to the normal type of epithelial growth is often seen in the arrangement within the alveoli of groups of cells around small spaces representing lumina. The following classes of carcinoma may be distinguished, depending upon the type of epithelial tissue from which the tumor has arisen.

**EPIDERMOID CARCINOMA** arises from squamous epithelium. It is characterized by an invading growth of the epithelium and a tendency to the formation of concentric masses of keratinized cells in the interior of the alveoli called pearls. Each mass of epithelium to a certain extent repeats the structure of the epidermis. On the outside is a layer of epithelium similar in character to the malpighian layer. The nuclei are oval with the long axis perpendicular to the surface, and with abundant chromatin; nuclear figures are numerous. Next to this layer come several layers showing a marked development of the intercellular bridges followed by a central mass of keratinized cells. The degree of keratinization varies greatly in the different tumors. The tissue affected being open to observation, the development and growth of this tumor has been closely followed. The tumor often is preceded by an active growth of epithelium and an increased thickness of the horny layer forming slightly projecting masses. Such a condition may exist for some time before the strictly carcinomatous growth begins, this often being preceded by an intense infiltration of the corium with lymphoid cells. The growth, as a rule, is less rapid than that of the glandular carcinoma, metastases occur less early and are usually confined to the lymph nodes. A variety of this carcinoma is known as the baso-cellular type from the erroneous idea that the tumor arises from the basal epithelial cells of the epidermis. The cells in this are small, often cylindrical, closely packed and of the same character throughout. There are no prickle cells and there is no formation of epithelial pearls. The alveoli are large, and the interlacing network which they form is very evident. Epithelial fibrils in great numbers may be present in the alveoli. These tumors are of very slow growth, there is little tendency to invade, they do not form metastases, and they may be multiple. With necrosis and destruction of the overlying epidermis, a very

chronic, slowly extending, superficial ulcer (rodent ulcer) results. It has been supposed from the abundant fibril formation that the tumor has its origin in the hair follicles. It is difficult to believe this in view of the fact that the rapidity of growth of a tumor is largely influenced by the growth capacity of the tissue from which it arises and there are few tissues in the body with such growth capacity as is shown by the hair follicles.

**GLANDULAR CARCINOMA**, a carcinoma having its origin in glandular epithelium, the type of the tumor appearing in carcinoma of the mamma. This tumor is so common and so frequently investigated that general descriptions of carcinoma are, in large measure, based upon it. The character of the tumor varies greatly.

**CYLINDRICAL CELL CARCINOMA**. Carcinomata which develop from cylindrical epithelial cells retain this cell type to a remarkable degree. These cells tend to grow in contact with the long axes parallel. The alveoli are very generally hollow, or if they contain cells in excess of those lining the walls, these are disposed in the interior in rows. Not infrequently there may be several layers of the lining cells. In the more rapidly growing parts of the tumor, the cells may lose the definite cylindrical type, becoming cuboidal or irregular and growing in the alveoli in solid masses. The prevailing arrangement of the cells around a lumen resembles the cell arrangement in adenoma and these tumors have been called *adenocarcinomata*, but the resemblance to the adenoma does not go further than the cell arrangement. There is no definite limiting membrane separating the epithelium from the stroma, and the tumor in all other particulars resembles the carcinoma.

Another form of carcinoma called colloid or, more properly, mucoid carcinoma results from the abundant formation of mucin, both in the tumor cells and the stroma, which gives to the tumor a transparent, gelatinous appearance. Formerly they often were called alveolar carcinomata, because the alveolar structure was more prominent in them. The cells are found in all stages of mucoid degeneration and often alveoli filled with dense mucus result from the total transformation of the cells. The colloid carcinoma most frequently originates from mucous membranes.

**CHORIO-EPITHELIOMA**, a tumor of peculiar type which in its typical form develops from the villi of the chorion. The tumor

has a relation to the formation of the uterine or hydatidiform mole and in about half the cases is preceded by this condition. In the mole formation, the villi become enormously enlarged by the accumulation of fluid, often with an excess of mucus, in the connective tissue. With this there is almost invariably considerable growth of the covering epithelium. In the chorio-epithelioma both layers of the covering epithelium proliferate. The syncytial layer is a covering protoplasmic mass, the cytoplasm dense, the nuclei placed at intervals. The layer often projects in the form of round or polypoid masses containing great numbers of nuclei. The Langerhans' cell layer below this is formed of cuboidal cells with clear cytoplasm and large vesicular nuclei and numerous nuclear figures. There is an irregularly disposed vascular stroma, but the cell masses for the most part grow freely in the blood sinuses without any stroma. The tumor has the power of invading and destroying tissue, the growth being chiefly within vessels and the metastases principally in the lung. Tumors in all respects similar in character may appear in other parts of the body as in the testicle, ovary, vagina, liver and peritoneum. In the ovary and testicle they usually are found in combination with teratomata and it has been assumed that a chorion has been produced in the teratoma in which the tumor has developed. The essential feature of the tumor is the peculiar form of epithelial growth and it is not impossible that this may occur in other forms of epithelium.

**HYPERNEPHROMA.** Tumors derived from the adrenal glands (hypernephron) usually are considered together. They are epithelial tumors and the adenomatous, papillary and carcinomatous forms may be represented. In the simplest form they appear as small circumscribed masses in the cortex, or in the capsule of the adrenal gland, or in similar positions in the kidney. The cells are large, pale, vacuolated, and contain fat and glycogen. They resemble most the cells of the glomerular layer of the adrenal. The tumors which are more atypical in the character and in the arrangement of the cells form large masses usually developing within the kidney, with a marked tendency to hæmorrhage and to invasion of blood vessels, the organ becoming in great measure destroyed by the growth. The papillary growth is often pronounced, the papillæ extremely long, thin and without branching. The metastases are numerous and occur chiefly in the lung,



although they may appear in any part of the body. In the lung there often is a secondary extension of the metastatic growth into the lymphatics which can become filled with the tumor. Tumors of similar character and evidently originating in embryonic adrenal inclusions may develop on the lower border of or within the liver.

## TERATOID TUMORS

These form a class of tumors of varying structure, in some cases simple, in others of great complexity, differing radically from the tissue in which they arise. This class of tumors has some relation to monster formations and more than any other tumors can be referred to errors in development resulting in a misplacement of embryonic tissue.

THE EPIDERMOID CYST is the simplest of these tumors. This is a small cystic tumor which is most frequent in the scalp, but may appear in the cutis in other parts of the body. It is lined with a simple, thin layer of epidermis without papillæ and without any epidermic structures, and is filled with a mass of butter consistency, containing fat, epidermic scales and cholesterin. It is due to separation and inclusion of epidermis during the development of the skin. THE CHOLESTEATOMA represents one form of this tumor. Like the epidermoid, it is composed of a cyst wall with an epidermic covering and contains a mass composed of horny adherent epidermic scales and often cholesterin. The contents have a peculiar pearly lustre. The most common situation of this tumor is at the base of the brain. Its presence here is to be referred to inclusion of epidermic cells at the period of closure of the medullary canal.

DERMOID CYSTS. These are cystic tumors in whose walls all the epidermic structures are found. In the contents of the cysts hair and sebaceous material may be found. These tumors occur by preference in relation to the anterior middle line of the body, especially in regions where the embryological development is complex. The tumor may be multilocular, secondary cysts being formed from the primary. Unlike the epidermoid, the connective tissue on which the epithelium rests forms a true part of the tumor. Here the inclusion is not of epidermis alone, but of the embryonic true skin. Cases are recorded in which epidermoid carcinoma has developed from the wall of such a cyst.

THE TERATOMATA are still more complicated, and often are very highly developed tumors. In these, tissues arising from the three layers of the embryo always are found, and in some practically all

the tissues of the body may be represented. They always are, to greater or less extent, cystic and not infrequently are multiple. Their most common situation is in the ovary. The two types found here are: (1) a single cyst containing hair and sebaceous material with an elevation at one part of the wall to which teeth are attached. The teeth may be numerous representing all forms and may also be found in the cyst contents. They are attached to a bone structure often resembling a part of the jaw and, in the soft tissue in the vicinity, small cysts or canals lined with cylindrical epithelium will be found; (2) a tumor, often of rapid growth, more solid in structure, but containing a number of small cysts. Not only do we find in these tumors many different tissues, but definite organs may also be formed. Nervous tissue in the form of neuroglia is very common and sympathetic ganglia with nerves, cerebellar and cerebral tissue may be found. Some of the cysts evidently are of ependymal origin lined with ependymal cells and surrounded by neuroglia. Canals representing the intestine with mucous, sub-mucous, and muscular layers are found. The teratomata also appear in the testicle, in the peritoneal cavity, in the sacrococcygeal region and within the skull. They may be congenital or develop later in life, often at the time of puberty. Metastases are seen infrequently. In these only certain of the tissues represented in the tumor appear. There have been a number of theories in explanation of these tumors: (1) that they are due to the inclusion of an undeveloped embryo within the tissues of a developing embryo; (2) that they are due to inclusion of polar bodies; (3) that they are due to the inclusion of blastomeres at an early period of segmentation when these cells still possess the potentialities of complete development.

**MIXED TUMORS.** More or less related to the teratomata is the class of mixed tumors. In these, various tissues are represented, but there is never the coördination among them leading to typical structures such as is seen in the teratomata. Their origin is to be referred to the inclusion of embryonic structures. In certain of them the tissue of the tumor remains of embryonic character, and to these the name embryoma might fitly be applied. They differ also according to the situation in which they appear.

Mixed tumor of the kidney always is congenital or appears early in life, usually before the fifth year. It is a tumor of the kidney

and is enclosed in the capsule of the organ. It often grows rapidly and may produce metastases. The structure is very characteristic. It consists of a stroma of cellular fibrous tissue which may contain striated muscle fibres and masses of cells of indifferent embryonic character. Within these masses are gland-like tubules seemingly formed by the cells. In other places there is not such a definite gland-like formation, but cell rosettes somewhat resembling the rosettes in the neuro-epithelioma of the retina are seen. In a few cases small cysts lined with epidermis and forming keratinized pearls have been described. These tumors generally are regarded as due to the inclusion in the kidney of a part of the wolffian body, or a tissue even more primitive than this.

Mixed tumor of the parotid gland is a much more common type of mixed tumor which occurs in the region of the parotid gland. These tumors are smooth on the surface, often greatly lobulated, the lobules extending deeply into the gland, thus presenting difficulties of removal. On section they contain islands of hyalin character, often islands of osteoid tissue or true bone, myxomatous tissue, and peculiar masses and strands of cells which extend in all directions. Cysts lined with these cells often occur. There has been much dispute as to the nature of the cells in the strands, whether epithelial or endothelial in character. The latter seems more probable. Similar tumors are found rarely in the sub-maxillary region and also are referred to an inclusion of embryonic tissues.

#### A CASE OF EPIDERMOID CARCINOMA OF THE LIP

Male, white, age sixty-three. For several months past has had a sore on the lip. Two years ago a hardened scale appeared which he picked off. This was repeated several times, a sore finally developing at the point. Has smoked a pipe for years.

Received for examination a V-shaped piece of tissue 3 by 2.5 by 1 cm. together with some loose tissue containing lymph nodes. The larger piece of lip tissue shows on one side shaven skin, on the other smooth, pale mucous membrane. In the middle of the upper surface at the junction of skin and mucous membrane, is a small superficial ulcer, irregular in shape, 6 by 5 cm. The tissue beneath and in the vicinity of the ulcer is indurated and immovable. On section through the ulcer a gray, rather opaque tissue continuous laterally with the epidermis is found beneath it. This tissue is from 1 to 2 mm. in thickness, the lower border not being distinct.

One of the lymph nodes shows on section a small opaque grayish area about 2 mm. in diameter, situated in the periphery. The two other small nodes are normal. The rather loose reddish tissue is found to be submaxillary gland.

#### A CASE OF CARCINOMA OF THE OESOPHAGUS

Anatomical diagnosis. Ulcerated constricting epidermoid carcinoma of oesophagus with extension to trachea and into a cervical lymph node. Communication between trachea and oesophagus through the tumor extension into trachea. Tuberculosis of left lung with cavity formation and tuberculous pneumonia. Tuberculosis of mediastinal lymph nodes. Chronic and acute bronchitis. Congestion of lungs. Chronic fibrous mitral endocarditis. Arterio-sclerosis. Chronic fibrous perihepatitis. Passive congestion of liver. Chronic interstitial pancreatitis. Slight chronic nephropathy. Double renal pelvis on right side. Focal hydro-nephrosis on right side due to impacted calculus in lower renal pelvis. Accessory adrenal gland.

Clinical history. Male, white, age fifty-two. Admitted to hospital three months before death, complaining of emaciation, loss of strength and difficulty of swallowing. Became progressively worse, developed a moderate temperature elevation more marked in the evening. Cough and expectoration profuse. No tubercle bacilli in sputum. A stricture of the oesophagus was located at a point 23 cm. from the line of the teeth and an ulcerated area demonstrated by the oesophagoscope.

Body of medium size, greatly emaciated, weight eighty-five pounds. Teeth carious. Moderate rigor mortis. Abdomen scaphoid. Slight oedema of ankles. Subcutaneous fat very slight in amount. Muscles pale.

Abdominal cavity dry. Slight adhesions in ileocaecal region. The appendix densely adherent to ascending colon. Marked ptosis of transverse colon, this lying 6 cm. below the umbilicus.

Spleen, weight 100 grams, adherent to diaphragm at upper pole. Capsule wrinkled and slightly thickened.

Adrenal glands normal. 1 cm. anterior to left adrenal is a small flat accessory gland 1 cm. in diameter.

Left kidney, weight, 150 grams. Capsule slightly adherent. On section consistency increased. Cortex 5 mm. in thickness, markings obscure. Pyramids distinct. Slight increase in pelvic fat. Right kidney, weight, 110 grams. Densely adherent to surrounding tissue. Lower pole distinctly shrunken and separated by a linear depression from the main part of the organ. Capsule adherent. On section there is a cyst in the lower pole 3 by 2.5 by 2 cm., containing a thin, cloudy,

reddish-brown fluid. On the inner surface there are numerous saccular diverticulæ corresponding to the pelvic calices and at one point a circular depression containing a calculus 1 by 1.5 cm. in diameter. There is no communication of this cyst with the pelvis nor with the ureter. The upper portion of this kidney shows the same condition as the left kidney.

Bladder normal.

Liver, weight, 1250 grams. There are focal thickenings of the capsule over the convexity, stellate in shape with communication between the branches. These do not extend into the liver substance. On section the hepatic veins and centres of lobules are congested.

Pancreas, normal in size, very firm, cuts with increased resistance; the cut surface shows very marked lobulation.

Stomach and intestinal tract normal.

The right lung adherent to pleura by stringy fibrous adhesions. Weight 560 grams, voluminous, congested. Drops of pus can be squeezed from the bronchi. There is moderate congestion of the bronchi and a considerable amount of adherent, viscid, purulent mucus. Left lung adherent at apex, weight 650 grams. Marked congestion of the tissue. In the apex a cavity 5 cm. in diameter, the inner surface roughened, the wall composed of dense fibrous tissue. Cavity contains a considerable amount of thick, viscid, yellow fluid, smears from which show tubercle bacilli. In the upper lobe adjoining the cavity there is a yellow gray solidified area which in places has a gelatinous appearance. A similar area is in the adjoining upper portion of the lower lobe. In the middle of the lower lobe posteriorly a pea-sized encapsulated mass of caseous material. Tissue elsewhere is the same as that of right lung. Lymph nodes at the bifurcation of trachea are enlarged, the mass composed of them measuring 5 by 4 cm. On section these are pigmented and contain grayish white caseous nodules.

Pericardium normal.

Heart, weight, 280 grams. Left ventricle firmly contracted, wall 15 mm. thick. Left auriculo-ventricular ring, 8.5 cm. in circumference, shows thickening of the ring, retraction of valve leaflets and thickening along line of closure. Chordæ tendineæ are thickened and shortened and the apices of papillary muscles are fibroid. The aortic orifice measures 8 cm., the valves slightly thickened.

The aorta shows throughout its length plaque-like yellow thickenings of intima.

Mucous membrane of mouth, pharynx and larynx normal.

Œsophagus shows extensive ulceration beginning at a point 2 cm. below the arytenoid notch and extending for a distance of 9 cm. The ulcer for the greater part involves the entire wall. At the edge of the

ulcer the mucous membrane is thickened and elevated. In the centre of the ulcerated area there is a slight saccular dilatation and in the lower part an evident constriction of the lumen. The œsophagus is firmly adherent to the surrounding structures, particularly to the trachea and upper part of the arch of the aorta and the larger vessels of the neck. On the left side one of the lower cervical lymph nodes is adherent to the tumor which has extended into this.

Trachea. At a point 3 cm. below the cricoid there is a greyish yellow elevation of the posterior surface, the size of a split pea. By probing, a minute communication between the trachea and the œsophagus is found at this point; 1.5 cm. lower down is a similar elevation but no communication with the œsophagus. Elsewhere the mucous membrane of the trachea is normal and a considerable amount of tenacious purulent mucus adheres to it.

REMARKS. The main points of interest in this autopsy are: First, the carcinoma of the œsophagus with its extensions into trachea and into one of the lower cervical lymph nodes. It is rather unusual that there were not found more metastases, particularly into the lungs and liver. The bronchitis is probably to be attributed to infection of the lung by means of the communication between the trachea and œsophagus. The great emaciation of the individual is due to malnutrition brought about by the constriction of the œsophagus. Such physical interferences with nutrition are the most prominent causes of the cachexias of the malignant tumors. Second, the tuberculosis confined to one lung producing cavity formation and tuberculous pneumonia with extension into the mass of lymph nodes at bifurcation of the trachea. In this connection also the absence of tubercle bacilli from the sputum is interesting. There was a profuse discharge from the bronchi, due to the bronchitis and the examination may have been of material from this source and not from the tuberculous cavity. Third, the congenital malformation of the kidney shown in the double pelvis. The hydronephrosis is confined to the region of one pelvis and is due to the blocking of the outlet by the calculus. Fourth, the chronic endocarditis of the mitral valve with some resulting contraction of the valve. This condition was not sufficient, however, to have seriously interfered with the work of the heart.

## A CASE OF CARCINOMA OF BREAST

The specimen consists of breast with a large amount of muscle beneath, and, extending from this, tissue to which numerous lymph nodes are attached. The nipple is retracted. Four cubic centimeters from the nipple is an elevated nodule, firmly attached to the skin. On section this is oval in outline 1 by 0.6 cm. in diameter, firm, of pearly gray color, with opaque points. It is firmly attached on all sides and passes without demarkation into the corium. Section of the breast through the depressed nipple shows a tumor mass taking the place of the mammary gland. The tumor is dense and hard, cutting like cartilage, of a general pearly gray color, with small, whiter and more opaque points. The mass of tumor tissue is oblong, the long axis parallel with the surface, measuring 6 by 3 cm. in greatest diameter. The tumor cannot be separated from the adjoining tissue, the edge is irregular and processes from the tumor extend into the surrounding tissue and upwards toward the nipple which is firmly adherent to the tumor. The tumor also adheres to the underlying pectoral muscle. In the fat tissue of the mamma 2 cm. from the tumor is a firmly adherent small gray tumor 1 cm. in diameter. On scraping the cut surface with a knife a small amount of opaque thin fluid is obtained. This, on microscopical examination, shows numerous epithelial cells of various size and shape, single and in groups and containing numerous fat drops. The adherent mass of axillary nodes shows one of these converted into a hard gray tissue and two of the others, on section, show small circumscribed areas of the same tissue.

The frozen sections of the tumor and the axillary nodes show in the breast a carcinoma of the medullary and scirrhous type and metastatic tumors of the same character in the lymph nodes.

**REMARKS.** This is a case of advanced carcinoma of the breast with secondary nodules in the surrounding tissue and with metastases in the lymph nodes. In a case so advanced as this complete removal of all the tumor cells can hardly be expected even in so thorough an operation as was done.

A CASE OF DEATH FROM CARCINOMA OF BREAST WITHOUT  
OPERATION

Anatomical diagnosis. Carcinoma (*en cuirasse*) of both breasts with infiltration of anterior thoracic wall. Extensive ulceration. Extensive pleural metastases. Metastases and extensive infiltration of axillæ. Single metastases in cerebral cortex and in lung. Chronic adhesive



pleuritis. Old tuberculosis of apices of lungs. Œdema of lungs. Myoma of uterus.

Body that of a white female, fifty-seven years old, of good physique and good nutrition. There is a very extensive ulceration involving the greater portion of the right upper breast and extending up over the shoulder and upper fifth of the anterior surface of the right arm. The ulcerated surface is rough and covered with much necrotic, foul-smelling tissue. The edges are indurated and beyond these the skin shows numerous pale-blue elevations varying in size from 2 to 8 mm. The overlying skin is adherent to these nodules. Similar nodules also extend widely beyond the edge of the ulcer, that is, from the right shoulder, anterior portion of right arm, right axilla, across median line covering left breast, portion of left shoulder and upper arm into left axilla, and beyond this reaching to anterior border of left scapula. The left nipple is absent and in its place is an ulcer 7 cm. in diameter, smaller, but of the same character as that on the right side. Section through the left breast shows an extensive infiltration with a firm pink gray tissue infiltrating fat, pectoral muscles and in places extending into the intercostal muscles. There is very marked œdema of both upper extremities and shoulders. No œdema in lower extremities.

Abdominal fat 3 cm. in thickness. In peritoneal cavity no excess of fluid, surface smooth with the exception of slight adhesions around the gall bladder.

The anterior wall of thorax shows extensive infiltration of all the tissue with the tumor masses. The right axilla is filled with a large mass of tumor, the axillary vein thrombosed, the nerve plexus embedded in the tumor mass, which, to some extent, extends along the nerve trunks. In the left axilla the vein is surrounded by tumor, but the nerve plexus is not so extensively involved.

Both pleural cavities show an increased amount of fluid. There are a few adhesions at the apices. Beneath the anterior parietal pleuræ there are numerous flattened, slightly elevated, gray nodules from 2 to 6 mm. in diameter.

Pericardial cavity normal. Heart weighs 250 grams. Myocardium and valves normal. Lungs show cicatricial thickening at both apices corresponding with pleural adhesions. Lower posterior portions are congested and contain much fluid. In the right lung posteriorly immediately beneath pleura there is a small gray nodule 8 mm. in diameter.

Mucous membrane of mouth rather pale. Pharynx, larynx, trachea and œsophagus normal.

Liver, spleen, pancreas and kidneys show no change other than slight post-mortem discoloration. In aorta a few slightly elevated, small,

yellow plaques most marked in abdominal portion. The lymph nodes with the exception of axillary show no change.

Stomach and intestines normal.

Uterus small, contains posteriorly a small intramural myoma, 3 cm. in diameter.

Calvarium and scalp normal. The dura is intensely adherent to calvarium; 3 cm. behind the fissure of Rolando and 2.5 cm. from the longitudinal fissure on right side is a single grey-white, slightly elevated tumor 1.5 cm. in diameter. On section it is sharply circumscribed. The brain is of uniform, firm consistency.

**REMARKS.** Of interest is the great local extension of tumor with ulceration. The tumor probably was primary in right breast, the left representing an extension. All of the lymphatic vessels in the region are involved. The direct extension of the tumor through the chest walls to the pleura is not very unusual. The metastasis in the lung may have been hæmatogenous in origin or the visceral pleura may have been invaded from without and the tumor extended into the lung. The cerebral tumor represents a metastasis by the blood stream. It also is rather striking that the metastases are not more numerous. The oedema of both upper extremities is due to compression of axillary veins by the tumor mass about them. On the right side this was accentuated by the thrombus. Of interest also is the general good nutrition, the absence of cachectic condition. In such cases we should expect to find extensive amyloid infiltration. We must assume that in cases such as this the body establishes an immunity against the toxic substances which must have been absorbed from the extensive sloughing ulcers.

**CLINICAL HISTORY.** The patient, a female, age 38, entered Huntington Memorial Hospital April 27th, 1912. She stated that a lump appeared in left side of abdomen seven years previously. This grew slowly and a year ago it began to cause pain. She entered the Massachusetts General Hospital, June 19, 1911, and the following day an operation was performed consisting in a median incision 5 inches long into the abdomen above the umbilicus. On palpating the stomach after the incision a firm, hard tumor as broad as the palm of the hand was found which involved the posterior wall of the stomach. The growth had extended through the posterior wall and could be seen on lifting the stomach as a small nodular excrescence about 1 cm. in diam-

eter. The diagnosis of carcinoma was made and gastro-enterostomy performed, a loop of jejunum being united to anterior wall of stomach. Patient remained four weeks in the hospital.

The lump in the abdomen continued to grow slowly and became painful especially after exercise. On February last she had an unusually severe attack of pain in left side of abdomen which extended to left leg. Since her operation she has been able to take liquids and soft foods only and has been much troubled by indigestion. The remote and family history of patient are negative.

On admission into Huntington Memorial Hospital patient appears as a well-built but rather emaciated female. Skin and mucous membranes pale. Lungs negative. Heart — the cardiac area normal. At the apex a short blowing murmur is heard accompanying the first sound. The abdomen is soft and depressed. Pulsation of abdominal aorta can be seen and palpated. In the median line between ensiform cartilage and umbilicus is a linear cicatrix, at the central point of which is a small, red elevated nodular area resembling granulation tissue. Beneath the upper end of the cicatrix an irregular hard area, approximately 4 by 3 cm., can be felt. There are numerous ill-defined masses to be felt in the gastric region. The epigastric region is somewhat full on percussion and resistant to the touch. The hepatic dullness extends from the seventh rib to two finger breadths below the costal margin. At the costal margin along the inner axillary line a rounded, firm mass, approximately 4 cm. in diameter, can be felt. Splenic dullness is not enlarged. Kidneys are palpable.

During the patient's residence in hospital the nodule in the cicatrix rapidly increased in size and the palpable masses beneath the upper margin of the abdominal cicatrix appeared to enlarge. She complained of burning and gnawing sensations in the stomach. There was, at times, very considerable abdominal distension, chiefly after eating. On June 24 patient vomited large blood clots and bloody fluid, and June 25th had a large bloody stool. The abdominal pain increased and note on July 19th states that "the attacks are frequent, very severe and come on without warning. During an attack the abdomen becomes rigid and the intestines can be felt to contract strongly and then relax." At this time there was noted a number of minute subcutaneous nodules over the abdomen. The pain and emaciation continued and slight oedema of the hands and feet developed. Patient died July 30th, having been practically moribund for five days before death.

Blood examination during her stay in the hospital showed a progressive diminution in blood cells and hæmoglobin. The last count on July 15th showed red cells 2,520,000 and hæmoglobin reduced to 35

per cent. During her entire stay in the hospital there was a slight and irregular elevation of temperature, practically not extending beyond 38.7° C. On July 24th began a considerable rise, extending on the 27th to 39.7 with a gradual fall to 37.8 before death, which occurred July 29th.

**Anatomical diagnosis.** Carcinoma of stomach with metastases to liver, adjacent lymph glands, omentum, pancreas, adrenals, peritoneum, small intestine, ovary, abdominal wall, ribs and sternum; Occlusion of pylorus; Gastro-enterostomy; Chronic fibrous pleuritis; secondary anæmia; Hyperplasia of bone marrow; Fatty degeneration.

**Autopsy.** The body is that of a well-developed and greatly emaciated white woman. There is a moderate degree of rigor mortis. The abdominal wall is retracted and presents in the region of the epigastrium a mass covered with skin measuring 6 by 5 by 5.5 cm. elevated 4 cm. above the surface. From the lower border of this mass there is a smooth, linear scar extending 3 cm. in the direction of the umbilicus. There is also an indurated and slightly elevated area 5 cm. across, which extends from the costal margin toward the umbilicus. On the inner aspect of the right leg there are a number of tortuous firm veins. Subcutaneous fat very small in amount, muscles pale.

**PLEURAL CAVITIES.** Contain no fluid; the surface of the superior lobe of the right lung is adherent everywhere to the wall of the thorax, but adhesions are readily broken.

**PERITONEAL CAVITY.** Contains 400 c.c. of yellowish, watery fluid. The mass presenting externally in the epigastrium is found to involve not only the abdominal wall, but the round ligament of liver. On section the interior of this mass is somewhat softened, and on pressure a soft, puriform material exudes. The edges of the liver extend beyond the umbilicus and numerous tumor nodules are seen in it. The right ovary contains numerous cysts and is infiltrated with tumor tissue. A loop of the jejunum is adherent to the lower portion of the anterior wall of the stomach and the transverse colon runs posteriorly to this. There is a flattened nodule in the omentum, measuring 1.5 cm., and several smaller nodules.

**PERICARDIAL CAVITY.** Contains a small amount of fluid.

**HEART.** Weight 172 grams. On its anterior surface is a nodule 0.8 cm. in diameter, of firm consistency and pale pink color. In other parts of the myocardium are several other small modules of similar character. The heart valves are normal.

**LUNGS.** Negative.

**INTESTINES.** Beneath the mucosa of the small intestine is a minute nodule 3 mm. in diameter. The intestinal canal is otherwise normal.

**SPLEEN.** Weight 183 grams. Somewhat pale and softer than normal.

**PANCREAS.** Is small; attached to the tail is a tumor nodule, measuring 1.8 cm. in diameter, of the same character as the tumors elsewhere.

**LIVER.** Weight 3131 grams. The large organ is infiltrated with tumor tissue. The tumor masses vary in size from  $\frac{1}{4}$  cm. to 12 cm. in diameter. The larger nodules are definitely umbilicated with deep depression in the centre and elevated edges. On section the tumor tissue is a pale gray color with pink tinge. The interior of the large masses is necrotic. The liver substance is pale. The markings are indistinct. The liver is adherent to the stomach and transverse colon. The gall bladder and ducts are normal.

**STOMACH.** The pyloric portion of the stomach is involved in a tumor growth which extends 7 cm. from the pylorus and appears as an irregular mass involving the wall. The central part of the mass is softened and the edges are irregularly elevated. The opening between stomach and jejunum is nodular at the edges. The pylorus is closed.

**ADRENALS.** The right adrenal contains a small tumor nodule 0.4 cm. in diameter, and in the left adrenal is a larger nodule 1.5 cm. in diameter.

**KIDNEYS.** Combined weight of kidneys, 257 grams. Between the peritoneum and the surface of the left kidney are a number of small, flat nodules the edges measuring 7 mm. The kidneys are pale but otherwise normal. The ureters are of normal calibre and patent throughout.

Bladder and uterus unimportant.

**OVARY.** The right ovary is replaced by a nodular mass of tumor tissue measuring 7 by 9 by 4 cm. Within this are numerous cysts filled with clear, yellow fluid.

**AORTA.** Normal.

Retro-peritoneal lymph nodes are enlarged, pale pink in color.

**BONE MARROW.** In lower end of femur the marrow is of a yellowish, translucent color. In the upper portion soft and red.

**BONES.** On the inner aspect of the sternum is a flat protuberance 4 cm. in length. The bone over the area is soft and crepitant and the interior is filled with reddish, soft tissue. There is a similar area in the lower portion of the sternum. The third rib on the right side presents a fusiform swelling extending 10 cm. from the sternal end. The swelling is 4 by 3 cm. in diameter and consists of a soft shell of bone which crepitates on pressure. The interior is filled with reddish, pulpy tissue. On the eighth rib is a thickened area, 4 cm. in length, of the same character as that in the third rib.

**BRAIN.** Weight 1205 grams. Convolutions are prominent, the sulci wide and deep, the general appearance resembling that of an atrophied brain of old age. The ventricles are negative.

**MICROSCOPICAL EXAMINATION.** The exudation in abdominal cavity contains a considerable number of large, rather pale cells of epithelial character, which are single or attached forming small groups. Sections of the stomach show the tumor to be a carcinoma which has infiltrated the entire wall. Section of the rib shows on the surface fibrous tissue enclosing alveoli of the tumor. The bone trabeculae are small and in places necrotic. About the necrotic bone there is a considerable formation of osteoid tissue with masses of tumor cells between the trabeculae. The process represents an extensive necrosis and destruction of bone with very imperfect renewal. Sections of the liver show great atrophy of the liver tissue, the tumor mass having the usual characteristics. Section of the tumor in epigastric region shows extensive tissue necrosis. The heart and kidney stained for fat show marked fatty degeneration. This is general and diffuse in the heart. In the kidney the degeneration is confined to the collecting tubules and ascending arm of the Henle loops.

**REMARKS.** There are many points of interest in the case. The age of the patient is rather below the age at which carcinoma of the stomach is most frequent. The statement of the patient as to the presence for seven years of a lump in the abdomen must be taken with a certain reserve; it is improbable that the process began so long ago. The gastro-enterostomy was performed to relieve the stenosis of the pylorus which the tumor produced. The disease at the time of operation was so advanced that radical removal could not be undertaken.

The emaciation of the patient is due in part to the interference with the function of the stomach, in part to the constant pain, and in part to the toxic absorption. The effect of this on metabolism is shown by the marked fatty degeneration of the heart and kidneys apparent on microscopic examination. The anæmia, another marked feature, is due to the malnutrition, to the hæmolytic action of toxic absorption, and to hæmorrhage from the tumor, which is shown by the vomiting of blood and the bloody stools. The red bone marrow of the femur is evidence of blood regeneration following the anæmia to which the cardiac murmur is also due.

The slight and constant elevation of temperature during her stay in the hospital is evidence of the effect of absorption of toxic products. The small size of the heart shows that this organ shares in the general atrophy of the body. The tumor in the stomach has the general character of carcinoma of the alimentary canal, necrosis and ulceration in the centre with wall-like peripheral growth. The area involved is large, the pylorus completely closed and the opening into the jejunum also encroached upon. The situation of the prominent subcutaneous tumor in the epigastrium in the line of the scar is probably due to the inclusion of tumor cells in the wound at the time of the operation. The growth of this during the last two months was very rapid. The growth of the large masses in the liver and in the primary tumor may have been equally rapid, but was marked by the central necrosis and absorption. The rapid growth and absorption are shown by the deep central depression in the liver metastases. The metastases are due chiefly to conveyance of the tumor cells by the blood stream. They are most numerous in the liver, as is to be expected. The bone metastases are more extensive than usual. These develop in the medullary cavity and as the tumor enlarges there is constant destruction and new formation of the surrounding bone. The old bone does not expand. In the present case there was a thin shell of bone over the tumor, which was partly necrotic and partly imperfectly calcified new bone; the rubbing of the spicules on pressure produced the crepitation. The tumor cells also passed into the peritoneal cavity as is shown by their presence in the exudation. The large tumor of the ovary is to be attributed rather to extension into this of a peritoneal implantation than to metastasis by the blood. The involvement of the lymph nodes is less marked than is usual.

#### A CASE OF MELANOTIC SARCOMA

Female, white, age thirty-two. A pigmented mole, size of nail of index finger, on back of neck in median line over spine of vertebra prominens. Eight months before induration was noticed about and beneath the mole. Since then growth has been progressive, at first slowly, lately more rapidly.

Received for examination an area of skin and subcutaneous tissue which contained a small tumor 2.5 cm. in diameter. This tumor is

firmly adherent to the overlying skin. On section the tumor is of firm homogeneous consistency, and of a mottled brown to black color. The tumor tissue passes into the epidermis over it.

Microscopically it consists of masses of cells with small strands of dense connective tissue between them. The connective tissue is small in amount, contains but few cells and seems to represent only the dense tissue of the corium separated by the cells. There are numerous large, thin-walled vessels in the connective tissue. In the seemingly separated cell masses single connective tissue fibrils and capillary vessels can be seen along which the tumor cells often are arranged as palisades. The cells are of much the same size, their shape influenced by mutual pressure. Most of them are free from pigment, others contain brown or black pigment in granular form. At the periphery the tumor cells infiltrate the tissue. There are numerous nuclear figures in the cells.

Diagnosis, melanotic sarcoma. Prognosis unfavorable.

#### A CASE OF SARCOMA OF PENIS

The following case is a sarcoma, unusual in situation and of malignant character. There are three laboratory records of the tumor. The first says: A small piece of tissue removed from a growth on the penis. Examination shows masses of spindle and irregular cells rather loosely arranged. In the masses are large vascular spaces. Diagnosis, sarcoma.

The next examination is of the amputated end of the penis. This showed a small tumor 3.5 by 1.5 cm. projecting into the urethra and attached to the lower surface of this over an area 1.5 by 1 cm. On section gray, of homogeneous consistency with a few irregular fissures. The tip of the tumor projects through the meatus and is necrotic. The urethra posterior to the tumor is dilated. Microscopical section through the tumor and adjoining urethra shows a covering of intact mucous membrane which is thickened where the tumor projects from it and infiltrated with lymphoid cells. At the base of the tumor there is marked infiltration with lymphoid cells. The tumor is composed of masses of spindle and irregular cells which contain numerous nuclear figures. There are numerous fissures lined with endothelium and many of these contain red blood corpuscles.

The third note is after four months. The entire penis and one inguinal lymph node were removed. At distal end of the penis is an elevated cauliflower growth extending backwards 2 cm. without sharp limitation. The lymph node removed is egg-shaped, smooth, 3 by 4 cm. in diameter.



Microscopically, the growth in the penis and lymph node shows the same general character of the tumor previously removed, but the cells in most places have a definite concentric mantel-like arrangement about the blood vessels. The vessels with the connected cell mantels can be pulled as strands from the affected lymph node. Prognosis unfavorable, further history unknown.

#### A CASE OF LYMPHOMA

Anatomical diagnoses. Lymphoma. Primary in lymph node. Metastases in liver, spleen, kidneys, adrenals, intestinal canal, lung, bone marrow and epicardium. Multiple hæmorrhages in skin, mucous membranes and epicardium. Enlargement of liver and spleen. Emphysema. Arterio-sclerosis. Cicatrix of lung.

White, female, age fifty-six years. Entered hospital April twenty, 1907. Loss of appetite and strength for last two years. Eight weeks before entrance lymph nodes of neck became enlarged. Two weeks later joints were swollen and painful. Subsided under treatment. At entrance purpuric spots present on legs. Dyspnea and a sore throat developed April twenty-one. Sputum very profuse, contained much blood. Increase of dyspnea up to time of death, April twenty-seven. Deafness appeared April twenty-one and became very much worse. On examination, pupils small and sluggish; exceedingly deaf. Enlarged lymph nodes in neck, axillæ and groin. Sonorous and sibilant râles in lung. Heart sounds weak. Liver enlarged. Area of dullness in left side suggesting enlarged spleen pushed down by liver. Dullness extended to two fingers breadths above the crest of the ileum. Liver and spleen tender. Over lower abdomen, labia and inner and outer portions of thigh scattered, minute, bright red ecchymoses. Elsewhere over body larger and darker ecchymoses. Blood count showed 16000 leucocytes, 40 per cent of lymphocytes.

Autopsy twelve hours after death.

Body is that of a middle age woman of large frame. Rigor mortis present. Subcutaneous fat abundant. Face, ears and hands cyanotic. Abdomen slightly distended. There are petechiæ over the arms and ankles most abundant about pubis and inner sides of thighs. Slight œdema of ankles. The cervical nodes on both sides are swollen and about the size of a pigeon's egg. One node palpable in right axilla, one in left. Inguinal nodes enlarged to about the size of an English walnut, soft, discrete and movable. On opening abdomen liver is enlarged reaching to 5 cm. above the umbilicus in the middle line. Spleen also enlarged. The intestines are injected, their walls thickened.

Peritoneal cavity contains small amount of clear fluid. Surface smooth and glistening. Lymph nodes along the lesser curvature of the stomach,

the peri-portal, the mesenteric and retroperitoneal are enlarged, those about the head of the pancreas being the most affected. The largest of these nodes measures 0.5 by 5 cm.

Thoracic cavity is free with the exception of a few slight adhesions. Pleural surfaces smooth. Lungs voluminous, everywhere crepitant except for a few small, semiconsolidated areas at the bases posteriorly. There is an irregular pigmented cicatrix at the left apex. At the bifurcation of the trachea is a mass of enlarged nodes varying in size from 0.5 to 4 cm. The vagi pass on either side of this mass and are not involved in it. The nodes at hila of the lungs and along the trachea also are enlarged. The mucous membrane of the trachea and bronchi injected, in places hæmorrhagic with grayish spots up to 2 mm. beneath the surface.

Heart. Weight 290 grams. Right side distended with pale clots which have a greenish tinge at edges and are more opaque than usual. There are ecchymoses beneath the epicardium of the right auricle. The wall of the right ventricle is 9 mm. thick, the left 1.3 cm. The edges of mitral and tricuspid valves are thickened. Aorta throughout shows numerous slightly elevated yellowish plaques.

Liver. Weight 2580 grams. Surface shows a white mottling. On section, white lines appear along the course of the portal vessels.

Spleen. Weight 535 grams, 15 by 6 by 9 cm. Pulp is soft, bright red in color. Surface shows a whitish mottling.

Pancreas. Normal.

Kidneys. Slightly enlarged, combined weight 330 grams. Cortex of normal thickness, yellowish, with indistinct markings and contains a number of white nodules up to 3 mm. in diameter, elongated, the long axis perpendicular to the surface.

Adrenals. Normal.

Bladder. Normal.

Uterus. Adenexa normal. A few small hæmorrhages in the vaginal mucosa.

Gastro-intestinal tract. The gastric mucosa is hæmorrhagic and the stomach wall contains numerous small nodules in its substance. The intestinal mucosa also is hæmorrhagic, the walls are thick, but there is no macroscopic hyperplasia of the lymphoid tissue.

Lymph nodes. The lymph nodes everywhere present the same appearance. They usually are discrete and encapsulated, soft, occasionally almost diffuent on section. The cut surface is smooth, homogeneous gray yellow and often mottled with hæmorrhage. Marrow from shaft of femur, ribs and vertebra pinkish red and soft.

Histological examination. Lungs. The scar at the apex composed of

pigmented cicatricial tissue in which are small cavities representing alveoli with thickened walls. In this area and in the vicinity are large numbers of round cells. In the thickened tissue there are greatly dilated lymphatics filled with cells of the large lymphoid type. The alveoli of the lung are generally large, their walls atrophic. There are numerous collections of lymphoid cells about the vessels and in the walls of the alveoli. The capillaries are dilated. In places the alveoli contain red corpuscles and desquamated epithelial cells.

Trachea. Shows great dilatation of the vessels of the mucosa with diffuse hæmorrhage. All of the vessels contain large cells of the lymphoid type sometimes among the red corpuscles, oftener in clumps. In some of the vessels are collections of fibrin enclosing in the meshes large cells. In the interstitial tissue between the vessels there are numbers of cells of the same lymphoid type both in masses and as a diffuse infiltration. The mucous glands of the trachea show a diffuse infiltration with the same cells, extending from this and in one place reaching up to the surface are tumor-like masses of the same large cells.

Stomach. Mucosa and submucosa infiltrated with small lymphocytes and few larger mononuclear and plasma cells with foci of hæmorrhage. There are collections of similar cells about the vessels.

Liver. A section stained with methylene blue and eosin shows to the naked eye blue masses in a more or less well-defined reticulum extending between irregular reddish areas. Microscopically, the periportal tissue contains numerous nodules in tumor-like form composed of masses of cells diffusely scattered in a slight reticulum. Similar though smaller nodules of the same tissue are found within the lobules. There is very slight infiltration around some of the hepatic veins. The capillaries are dilated; they contain red blood corpuscles, a few polynuclear cells and numerous cells of the lymphoid type. The cells in the tumor-like masses are irregular in outline, the cytoplasm small in amount staining slightly with blue; no definite granulation. The nuclei are large vesicular, with numerous chromatin granules and there are numerous nuclear figures. The cells show little variation in size. Measurement of twenty shows the average size of 8 by 5  $\mu$ . There is no direct extension of the cells of the nodules into the sinusoids of the liver.

Spleen. Shows a diffuse infiltration with large lymphoid cells.

Kidneys. There is a nodular infiltration of large cells at various places between the tubules of the cortex. There also are nodules where the tissue is almost completely substituted by the tumor cells, longitudinal tubules being found in these with no destruction of epithelium. Here and there the tumor cells have penetrated the membrana propria and are found beneath the epithelium. In the straight vessels of the pyra-

**mids** there are large collections of lymphoid cells. Very numerous similar cells are found in the capillaries of the glomeruli. In addition there is considerable thickening of the glomerular vessels and an increase in the cells between them.

**Heart.** The heart shows diffuse, in places nodular lymphoid infiltration of the epicardium and considerable hæmorrhage.

**Adrenal** shows nodular masses of tumor-like tissue with disappearance of the glandular tissue between them and extending out from this a diffuse infiltration between the tubules. No trace of gland tissue can be seen where the tumor tissue is most developed.

**Lymph nodes.** All these show the same change. The whole tissue of the nodes is substituted by a diffuse formation of the large round cells. In most places there is no evidence of capsule and the tumor growth extends from the glands into the surrounding tissue.

**Bone marrow.** The bone marrow gives the usual picture of an active marrow, but there are, in addition, foci where the marrow is entirely replaced by circumscribed collections of the same tumor cells as seen elsewhere.

**REMARKS.** A typical case of lymphoma with metastases. In regard to the numbers of lymphocytes, there is great discrepancy between the clinical blood count and the contents of the vessels. It is possible that the deafness was due to formation of lymphoid tissue in the internal ear.

#### A CASE OF MYELOGENOUS LEUKEMIA

**Anatomical diagnosis.** Myelogenous leukemia. Diffuse purulent infiltration of subcutaneous tissue of neck extending into parotid. Abscess of lung. Leukemic enlargement of liver and spleen. Hæmorrhages and infarction of spleen. Hæmorrhagic infiltration of intestinal mucosa. Primary tuberculous ulcer of ileum.

White, male, age twenty-seven years. Entered hospital complaining of general weakness which has been increasing for two years, and pain and swelling below the ear.

On examination, ill-nourished and pale, muscles atrophied. Mucous membranes pale, slight yellowish tinge in conjunctiva. Abdomen greatly enlarged. No evidence of ascites. Abdominal walls thin, liver dullness greatly increased, in erect posture, extending below umbilicus. Corresponding to lower border of dullness, the large rounded edge of the liver can be felt. The area of splenic dullness merges above into that of liver, extends laterally from mid-clavicular to mid-axillary line and below to the crest of the ileum. When the patient stands there is an

abdominal protuberance corresponding to this area. Heart action somewhat feeble and irregular, no murmurs. No dullness in lungs, a few râles at base on both sides. Has slight cough. On the left side of neck is an indurated, poorly defined swelling, most prominent behind the angle of jaw and involving an area about 5 cm. in diameter. At the apex there are three small ragged openings from which a thin sanguinous pus can be expressed. The urine contains albumen and numerous hyalin casts. The blood is pale; count gives leucocytes 825,000, erythrocytes, 2,900,000. Differential count, myelocytes, 50 per cent; polynuclear and transitional cells, 30 per cent; mono- and polynuclear eosinophiles, 8 per cent; cells of lymphoid type, 12 per cent; numerous nucleated red corpuscles. Temperature 102 degrees, pulse 90. During the following two days cough increased, with considerable dyspnea and cyanosis. Death on third day.

The body large, emaciated, slight rigor mortis. General surface pale, face somewhat cyanotic, oedema of ankles. On the left side of the neck is a large, indurated swelling in which, posterior to the angle of the jaw, there are several small ragged openings. On excising this mass there is found a diffuse purulent infiltration extending through it and into the adjacent tissue. The parotid gland on the left side is infiltrated with pus and contains necrotic masses.

Skin thin, subcutaneous fat yellowish, small in amount, muscles pale. Peritoneum smooth, contains a small amount of yellowish fluid. Liver and spleen enormously enlarged. The spleen occupies the left side of the abdomen extending from within the pelvis to the thorax. The liver in the mid-clavicular line extends 14 cm. below the costal border, in the middle line 13 cm. below the ensiform cartilage. Diaphragm on right side can be pushed to third intercostal space, on the left to the border of the fourth rib. All the vessels of abdominal organs greatly enlarged, the splenic vein 1.5 cm. in diameter and filled with a soft, friable, lilac-colored clot. The dilated portal veins contain similar clots.

Both lungs are slightly adherent posteriorly; crepitant for the most part, tissue heavier and denser than normal. On section pus can be squeezed from bronchi in lower lobes. In the lower lobes of both lungs there are several areas of consolidation surrounded by hæmorrhagic lung tissue, on section soft, containing pus in the centre. In one of these areas there is a ragged central cavity with projecting necrotic edges.

Pericardial cavity smooth. Right side of heart somewhat dilated, heart otherwise of normal size, right side and left auricle contain soft, rather friable clots. Valves normal, weight 325 grams.

Liver very large, weight 3400 grams. The superior inferior diameter of right lobe 26 cm., that of the left 16 cm. The lower border is thick

and round. Capsule smooth and tense. On section it is of a uniform pale yellowish-brown color. No nodules are present. All the vessels large. Organs firm but friable.

Spleen is adherent at a few points. It measures 28 by 18 by 9 cm. Weight 3100 grams. The capsule is tense and shows beneath it numerous discrete round or irregular very dark-red areas which vary from 2 mm. to 2 cm. in diameter. There are also on the surface several pale, opaque areas up to 3 cm. in diameter with irregular, sharply circumscribed edges extending irregularly into the tissue beneath. The spleen is firm, homogeneous save for the areas mentioned and of a pale grayish-red color. Several dark-red areas in the tissue correspond with those on the surface.

The kidneys are of usual size, weight 290 grams, capsule nonadherent, surface smooth. On section cortex pale, markings obscure. Pelves and ureters normal.

Gastro-intestinal canal; transverse colon and stomach displaced downward. Intestinal wall thickened. There are a few foci of hæmorrhagic infiltration in the mucosa of the ileum. No hyperplasia of the lymphoid tissue. In the ileum, corresponding to the situation of the peyers patch, the wall is thickened and shows on the surface an irregular shallow ulcer with a granular base. Section of intestine passing through the ulcer shows several opaque, apparently caseous areas extending to peritoneal surface.

The bladder contains a small amount of pale urine; the genitalia are normal.

The mucous membrane of mouth, pharynx and larynx pale. Tonsils and lymphoid tissue not enlarged. Œsophagus and trachea normal. Thymus not perceptible.

The lymph nodes, particularly mesenteric and retro-peritoneal, are slightly enlarged, pale and homogeneous on section.

Bone marrow everywhere of the same character. In femur the medullary cavity is enlarged and filled with a granular, friable, reddish, pale marrow which when removed contains no spicules of bone and leaves a smooth internal surface.

Scalp of ordinary thickness save for slight œdema in left side corresponding with the cervical swelling. Skull normal. Meninges non-adherent. Brain, weight 1240 grams, of ordinary consistency.

Cultures from the neck and from the lung gave numerous colonies of *staphylococcus pyogenes aureus*.

Microscopical examination. Sections from the tissue below the ear show purulent infiltration of tissue and abscess formation. The larger veins are thrombosed. The thrombi are composed principally of poly-

nuclear leucocytes with much fibrin. Among the cells large mononuclear leucocytes can be distinguished. All of the smaller blood vessels are very greatly dilated. The tissue is oedematous and there is a great deal of fibrin in the tissue interstices. Within many of the smaller vessels there are small, mural thrombi. In various places in the tissue there are definite abscesses with softening and complete disintegration of the tissue. The cells in these abscesses are exclusively polynuclear leucocytes. There also are masses of round cocci having the morphological characteristics of staphylococci. The purulent infiltration extends deeply into the muscles of the neck. In the ducts of the parotid gland there are numerous polynuclear leucocytes. Within the dilated blood vessels the principal cells are mononuclear with a round or oval, darkly staining nucleus, and finely granular cytoplasm. The next most common variety is a cell with an irregular, lobulated nucleus somewhat approaching in shape that of the polynuclear leucocyte, the entire cell and nucleus being much larger, the nucleus not so densely staining. The large cells have an average diameter of  $9\ \mu$ . The polynuclear leucocytes under the same conditions of measurement have an average diameter of  $6\ \mu$ .

Section of the lung through one of the small areas of consolidation shows a complete purulent infiltration of the tissue; in the centre the tissue is broken down, only fragments of alveolar walls being present. In the tissue nuclear fragments, evidently from polynuclear cells, and larger round masses of chromatin, seemingly derived from the nuclei of the large cells, are found. In the surrounding lung tissue there is considerable hæmorrhage, much fibrinous exudate and desquamated alveolar epithelium. In the intact lung tissue at a distance, the alveolar walls are very greatly increased in thickness, due to dilatation of the capillaries which are closely packed with cells similar to those described in the parotid region. There are very few polynuclear leucocytes among these cells. Measurements of the capillaries of the alveolar wall show diameters varying between  $20$  and  $10\ \mu$ . Numbers of nuclear figures are found in the cells within the capillaries.

Sections of mesenteric lymph nodes show all of the blood vessels greatly dilated and filled with cells of the same character as those described above. The lymphoid tissue is small in amount, the cells in the follicles are widely separated by oedema, the germinal centres are not evident. All of the sinuses are greatly dilated. They contain, in part, large cells of the same character as those in the blood; in part, large endothelial cells with characteristic nuclei, which often contain englobed lymphocytes. These large phagocytic cells are numerous, many of them very large and containing crystalline masses. These crystals are of brownish color.

They lie sometimes in vacuoles of the cells, sometimes simply enclosed in the cytoplasm; they occur both singly and in masses, are elongated octahedra and have an average length of  $6\ \mu$  and a width of  $1\ \mu$  (Charcot-Leyden crystals). The cells containing them are from 20 to  $30\ \mu$  in their long diameter.

Sections of liver show this to be in large measure completely supplanted by myeloid tissue. Within this there are here and there thin remnants of liver cells. There are a few areas where the structure of the liver is preserved. In these places the liver cells appear as a thin network between the greatly dilated sinusoids. There are comparatively few red corpuscles, the whole tissue being myeloid. There are numerous nuclear figures in the cells.

The spleen is homogeneous in character. There are no lymph follicles. The trabeculae are only here and there visible and do not seem to be increased in amount. The whole tissue is composed apparently of dilated blood vessels and sinusoids with a very marked general and diffuse increase in the connective tissue reticulum.

In a section of the kidney the blood vessels are dilated. The epithelium in the convoluted tubules is somewhat swollen, more granular and oedematous. The glomeruli show slight thickening of the capillary walls, the vessels are dilated and filled with the usual cells. Here and there in some of the capsular spaces there is coagulated albumin. An occasional hyalin cast is found in the tubules of the pyramids. The glomeruli are large, some of them measuring  $0.3\ \text{mm.}$  in diameter, but averaging about  $0.2\ \text{mm.}$

In the ulcerated area of the ileum there is a loss of substance extending below the muscularis mucosa. The blood vessels are very greatly dilated; between them there are masses of lymphoid cells, no definite follicles, and a few areas of definite caseation with giant cells and all the characteristics of tuberculous tissue. The cellular infiltration extends down into and through the muscular coat. In one section there are two or three areas of caseation with miliary tubercles about them which extend completely through the muscular coat. Search of this tissue for tubercle bacilli failed to reveal them.

**REMARKS.** This is a typical case of myelogenous leukemia. Of interest is the staphylococcus infection of the neck and the abscesses containing only polynuclear leucocytes. Of great interest also is the tuberculous ulcer of the ileum. Anatomically this is characteristic, and the fact that tubercle bacilli were not found does not vitiate the diagnosis. It is not always practicable in laboratory work to spend a sufficient time in such a search to detect



very small numbers of bacilli in tissues. The ulcer is acute and represents a very recent infection which, like the staphylococcus infection, was favored by the depraved physical condition of the individual. There must have been also a great increase in the total amount of blood. The abscesses in the lung were hæmatogenous in origin and associated with the infected thrombi in the vessels of the neck.

#### A CASE OF DOUBLE CONGENITAL TERATOMA

White, male child, born May 18th, pregnancy and labor normal. A tumor as large as a hen's egg was situated on the right side of the scrotum. This gradually increased in size, and was removed by operation June 8th. The outside of the tumor is smooth and oval in shape, measuring 7 by 5 cm.; it occupies the position of the testicle, and at one pole is a projection identified as epididymis. On section, consists of a solid stroma in which are small islands of cartilage and numerous cysts of various sizes, the largest cyst measuring 1 cm. in diameter, the smallest just visible to the naked eye. Microscopically there is a large amount of striated muscle tissue in the solid portion of the tumor, the fibres appearing both singly and in masses. The fibres are of the adult type and contain relatively greater numbers of nuclei than normal. The areas of cartilage are principally hyalin, some fibrous. Newly formed bone, containing both osteoblasts and osteoclasts, is found. The stroma in places contains large numbers of round and spindle-shaped cells, giving it a distinctly sarcomatous appearance. In other places there is a considerable amount of fibrous and mucoid tissue between the cells. All of the cysts are lined with epithelium. In some the wall is smooth, in others there are numerous papillary projections extending into the cavity. The character of the epithelium varies. In some cysts it partakes of the character of the skin and in others of that of mucous membrane. Some of the cysts are lined with a single layer of ciliated epithelium. In one cyst the epithelial tissue has the characteristics of that of the trachea and back of it are scattered mucous glands and cartilage. A portion of the lining of one cyst closely simulates the choroid and retina.

In January of the following year a swelling appeared in the right parietal region. On examination, a tumor mass was found connected with the skull, the skin movable over it. On January 15th, an operation was attempted and showed a soft tumor partly covered with bone and attached to the skull. This was detached leaving the skull rough and bare under it. The head at this time was enlarged. Following the operation it grew rapidly in size increasing 1 cm. in circumference daily.

Another operation was performed and a large tumor found inside of the skull. The tumor was not removed and the head continued to enlarge rapidly. Ulceration of the skin over the tumor took place in March, and several sinuses appeared, from which fetid pus was discharged. Death took place April 23, nine months after birth.

At autopsy a large tumor mass is found seated chiefly inside the skull, but projecting in numerous places through it. On its lower surface the tumor is attached to the dura mater, in no place extending through this. It weighs 1320 grams. It contains numerous cysts, some filled with clear, thin fluid, others with a thick gelatinous material. In many of them are hairs.

On microscopical examination, structures similar in character to those of the testicular tumor are found, but the nervous tissue is more fully represented. In neither tumor are any structures found which simulate either liver, kidney or spleen. Lymphoid tissue in definite arrangement and lymphoid vessels are found, but no tissue resembling marrow.

**REMARKS.** This is to be regarded as a case of double teratoma. The tumor of the skull can not be regarded as a metastasis. In both tumors the growth was rapid. It did not proceed from any one of the many elements in the tumor but seemed to involve all. It is possible that the growth was largely due to enlargement of the cysts from secretion of their epithelium. The growth of the tumor was not infiltrating. It grew as a mass. The projections through the skull were chiefly through the natural openings which had not become closed.

**EXPERIMENT.** The complexity of the experimental work in tumors makes it advisable to limit the student's work to the simple transplantation of an inoculable mouse tumor. An affected mouse is chloroformed, and the skin over the tumor laid back with aseptic precautions. Small pieces of the non-necrotic part of the tumor are placed in a special cannula, the obturator inserted so that the tumor makes its appearance at the sharp end of the cannula. The cannula is inserted subcutaneously at the posterior end of the back of a normal mouse and pushed forward subcutaneously until the point lies in the axilla. The obturator is pushed in so as to discharge the contents of the cannula, the skin is pinched about the end of the cannula and the instrument slowly withdrawn. The operation is repeated so as to inoculate ten mice, and their condition observed over several weeks.

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## INFECTIOUS DISEASES

These are diseases due to the entry into the body of living things, which, growing in the tissues and fluids of the body, produce injury. The infecting organism is a parasite and the infected body the host. Not all parasites are harmful except in a very narrow sense. Most of the surfaces of the body contain micro-organisms which either live as pure saprophytes in the excretory products or use up an unappreciable amount of body material. It is customary to make a distinction between infection and infestation, applying the latter term to the case in which large parasites live at the expense of the body, but on the surface, as the pediculi of the skin and the tape worm of the alimentary canal. But there is no sharp distinction, for an organism may at one period of its life infest a surface, at another invade the tissue as does the trichinella. Considered in its biological aspects, infection is adaptation of an organism to the environment which the body of the host offers. In certain cases the environment is very narrow; for example, when an organism is parasitic for a certain species only; in others the environmental adaptation may extend to a large number of genera. The organism can be fitted to a parasitic existence exclusively, or may find suitable conditions for existence outside the living body, in which case the parasitism is said to be facultative. When the adaptation is mutual, including both parasite and host, the condition is one of symbiosis. It is evident that this is the most favorable condition for the parasite, and the death of the host an unfortunate incident, in that the particular family branch of the parasite which is living harmoniously in the host may be cut off.

The infectious diseases form not only an important group in themselves, but, with the possible exception of tumors, all pathological conditions in the body are to a greater or less extent associated with present or past infections. Whatever the nature of the final disease, death, in the majority of cases, is preceded by and often the immediate result of a terminal infection. Chronic disease of the heart, of the arteries, of the kidneys, of the brain, often can be traced to an infection.

The infectious or pathogenic organisms can be divided into the bacteria, the moulds, the yeasts and the protozoa. Some metazoan forms are found, but they are of relative unimportance in human pathology. The bacteria form by far the most important group, if we consider the number and importance of the diseases which they produce.

THE BACTERIA according to form are divided into the cocci or ball-shaped, bacilli or rod-shaped, and spirilla or screw-shaped organisms. Certain bacilli, as the tubercle bacilli, may occasionally show branched and irregular forms instead of the simple rod. In general, the bacteria are monomorphic and the species distinct, although within the species there may be considerable variation. Each bacterium represents a single cell, but there is no distinct differentiation of nucleus and cytoplasm. It is probable that the bacteria have a definite cell membrane which may become swollen to form a capsule. Such capsule formation plays a rôle in the pathogenesis in that it affords protection to the bacteria. Capsule formation is most evident in bacteria which are growing in the body fluids. Many of the bacteria can move actively by means of cilia which may be attached on all sides, or at one or both ends. The investigation of bacterial diseases and the demonstration of bacteria in relation with the lesions produced, has been greatly facilitated by methods of staining. Most bacteria stain with the basic aniline dyes. Complex methods of staining are necessary with certain bacteria and special staining reactions form an important means of differentiation.

The mode of reproduction of bacteria is important in relation to infection. The most common mode is by simple division. In certain species, spores are produced which have a much greater resistance than the simple bacterial cell. Spores are only produced outside the animal body and by bacteria which are capable of saprophytic existence. The production of spores is important in preserving the life of bacteria and keeping up the possibilities of future infections under conditions when, without spore production, the species would die.; e.g., the bacillus of anthrax. Most of the pathogenic bacteria are parasitic exclusively, finding suitable conditions for existence in the living body only, or in special culture media at special temperatures, e.g., tubercle bacillus. Others are both parasitic and saprophytic, e.g., anthrax bacillus; others, while

generally parasitic, may, under suitable conditions, grow as saprophytes, e.g., typhoid bacillus; others, while generally saprophytic, occasionally become parasites, e.g., tetanus bacillus.

Bacteria produce injury by means of injurious and soluble substances which they form. Their mere physical presence and the amount of material which they withdraw from the tissues of the host probably exerts no deleterious effect. These soluble substances are called *toxins*, which are in some cases excretory products of the bacterial cells. The toxins pass into the culture media in which they are grown, and may be obtained by filtration and in a purer state by a variety of other methods. Certain bacteria, of which the diphtheria and the tetanus bacillus are the best examples, exert their pathogenic influence solely by means of such toxins, which are produced at the site of infection and absorbed. Other organisms when grown in a culture medium produce no dissolved toxic substances, but the toxic substance, *endotoxin*, is connected with the bacterial cell and set free by destruction of the cell. The best example of this is found in the typhoid bacillus. There is not, however, a definite distinction between toxin and endotoxin, for many bacteria produce both forms of poison. These bacterial poisons possess a more or less definite affinity for certain of the cells and tissues of the body. The toxin of the tetanus bacillus possesses such an affinity for the central nervous system; that of the diphtheria bacillus, for the lymphoid tissue; certain toxins, the hemolysins, attack the red and others the white corpuscles. It is probable that this selective action is due to some peculiarity of structure of the toxic molecule, physical or chemical, or both, which enables it to enter or combine with the specifically affected cells. Apart from both the toxins and the endotoxins, the protein substance of the bacterial cells may give rise to lesions. This substance has no specific toxic action; it produces various degrees of injury and exerts a positive chemotactic action on the white blood corpuscles. The lesions which are produced in bacterial diseases are due in part to the direct injurious action of these toxic substances and in part due to the effect produced in other parts of the body by the loss or perversion of function of important organs which are the seat of direct injury.

INFECTION takes place by the entry of bacteria from without through one of the surfaces of the body. These surfaces are to a

greater or less degree protected. The skin is protected by means of the impervious horny layer, by the constant surface desquamation and the cell movement from within outward. The protection is less complete at the openings of the sweat glands and hair follicles, particularly the latter, for the sweat is not a good culture medium and the direction of flow opposes entry. Infection by the route of the hair follicles is not uncommon, for bacteria may find a culture medium in the moist débris of the hair sheath and can multiply there and produce a primary injury. The conjunctiva has a rather high resistance to infection for most micro-organisms, the surface is smooth and the lacrymal secretion and movement of lids offer a certain amount of physical protection. Infection here by the gonococcus, the diphtheria bacillus and other organisms is not infrequent. The nasal passages are protected chiefly by motion of the cilia. Infection of this surface may take place by diphtheria, glanders, leprosy, and influenza bacilli, by the pyogenic cocci, and probably by other organisms. Infection of the middle ear most frequently occurs from the entry of organisms from the throat by way of the Eustachian tube. The mouth, although harboring quantities of organisms and often pathogenic forms, is a comparatively rare portal of entry. Actinomycosis, noma, thrush and occasionally tuberculosis may find a primary location in the mouth. The tonsils, particularly in children, offer a favorable site for infection. The crypts contain moist masses of epithelium which afford good cultural conditions for the diphtheria bacilli and the pyogenic organisms. The lungs are protected from infection by the moist surface of the bronchi and the strong outward currents produced by the action of the cilia. The increasing surface area and the rapid branching of the bronchial passages retard the movement of the respired air and favor the early lodgment on the moist surface, of organisms which have passed the guard of the nasal passages and the larynx. The presence and situation of the carbon pigment in the lungs and the cases of infection which take place show that these guards are not always effective. The lungs must be regarded as a susceptible organ in spite of the abundant blood supply, the ease with which emigration of phagocytes takes place, and the marked phagocytic power of the epithelium lining the alveoli. There is a further disadvantage in infections of the lung, due to the great surface and the opportunity

for the organisms to extend by means of the open communicating canals, the bronchi. Infection from the mucous membrane of the oesophagus is rare, owing to the thick epithelial covering and the smooth surface. The stomach is comparatively free from infection, its principal defence being the acid gastric secretion. Of all of the surfaces of the body, the intestinal canal holds the first place as a portal for infection. The genito-urinary tract is almost the exclusive seat of infection in the so-called sexual diseases and may be invaded by a number of other organisms.

Infection from the surface probably takes place in most instances by the bacteria finding, on the surface, conditions which permit their multiplication and the production of a local injury, from which point the further extension takes place. It is an important question whether or not bacteria can penetrate an intact surface, producing no lesions there, and be carried to other places by the blood and lymphatic vessels. Generally, it is assumed that this does take place, the organisms passing through the intact intestinal canal. Internal infections are seen with intact surfaces, but it is difficult to exclude the presence of minute and even microscopic lesions. The abundance of nuclear figures in the crypts of Lieberkühn show that destruction and exfoliation of the epithelial cells constantly is taking place and the surface may, in many places, be robbed of the protection afforded by the single layer of cells.

Infections from wounds depends much upon the character of the wound. If with the wound pathogenic organisms are placed within the tissue, and they find, in the necrosis of tissue produced in injury, a place for growth removed from the action of the tissue fluids, infection easily takes place. The care taken in modern surgery to bring parts in perfect apposition and to avoid constriction, which might result in necrosis, is of great importance in preventing infection. Infection rarely takes place from granulating surfaces; the abundance of leucocytes on and close beneath the surface, gives protection by phagocytosis; there is an abundant stream of exudation from within outward, which acts mechanically and subjects bacteria to the destructive action of the serum. Pathogenic organisms, especially the pyogenic cocci, may be demonstrated by culture on the surface of perfectly healthy and healing open wounds. The most favorable conditions for wound infection are found when organisms are carried into the tissue by the bites

of insects. Such inoculations may be made in many places, thus increasing the probability of infection.

**PHAGOCYTOSIS.** Apart from the various protective influences of the body surfaces and their accessories, the most obvious defense is by phagocytosis. In almost all of the lesions produced by bacteria, an exudate is produced with an abundant emigration of white corpuscles. Either the bacteria themselves or the necrotic tissue produced by their action, or both, exert a positive chemotaxis attracting the leucocytes to the part. The wandering cells take up the bacteria which become surrounded in the cell by clear fluid, in which they are broken up and disappear. Their destruction is a process of intracellular digestion. The leucocytes which are chiefly concerned in such bacterial destruction are the polynuclear. Phagocytosis by endothelial cells, both those of the blood and those formed in the tissues, takes place, but to a far less extent. It never takes place in cells of the lymphoid series. It has been shown that phagocytosis is facilitated by some alteration produced in the bacteria by the action of substances called *opsonins*, which are present in the blood and which are capable of increasing in amount during the course of an infection. The presence of bacteria within polynuclear leucocytes is not in itself a certain indication of phagocytosis. The gonococci, for instance, seem to find in the polynuclear leucocytes the conditions for existence and growth, and there is no evidence of their destruction. It is also by no means certain that the tubercle bacilli which so often are found enclosed in endothelial cells or in giant cells are destroyed.

**BACTERIOLYSIS.** The bacteria also are destroyed by the action upon them of soluble bactericidal substances contained in the blood. Such destruction is effected by the interaction of two substances, one of which in itself is inoperative, but the action of which is necessary in order that the substance which produces the destruction may act. This sensitizing substance is known as the amboceptor, the destructive substance as the alexine or complement. The separate action of these two substances can easily be tested since the amboceptor is thermolabile and is not destroyed by a temperature of 56 degrees, while the complement is thermostable and is destroyed by this temperature. The amboceptor probably is produced by the tissue cells; its amount may increase in the course of infection and its formation be stimulated. The



action of the amboceptor is specific. The presence of an amboceptor enables the complement to act on one species of bacterium but not on another.

**ANTITOXINS.** It has been seen that certain of the bacteria have little tendency to invade the tissues, but act by the production of toxic substances which are absorbed and have a specific influence on certain tissues of the body. Against the action of such toxins the body cells react by the formation of antitoxins which neutralize or destroy the toxins. The formation of these antitoxins may be brought about by the injection into an animal of toxins formed by the growth of the bacteria outside of the body. Such antitoxins have no injurious action on the bacteria themselves. Phagocytosis, bacteriolysis, and the neutralization of toxin by antitoxin will take place outside of the body in the test tube. The action involved in the destruction of bacteria is a general action, and takes place when any foreign cells are introduced into the body. It has been most studied and the clearest ideas have been formed concerning it, in the reaction of an animal to the injection of foreign red corpuscles. The hemolysis or destruction of the foreign corpuscles is effected by the interaction of amboceptor and complement, and by the injection of the foreign corpuscles in small numbers the amount of amboceptor can be greatly increased. Any substance which gives rise to the formation of antibodies is called an antigen.

**LESIONS PRODUCED.** The different organs of the body show great variations in the lesions produced. The best example of this is seen in tuberculosis. The skin offers a high degree of resistance to the action of the bacilli. The lesions produced are slow in development, circumscribed in character, there is but feeble growth of the organisms, and there is but little tendency to the degenerations so commonly associated with the action of the bacilli. The liver, while highly susceptible to attack, quickly acquires a high resistance, in it the lesions are numerous, circumscribed in character, and the bacilli so few that their demonstration is difficult. The voluntary muscles possess an almost complete immunity. The streptococcus infections of the skin also differ in character from infections elsewhere. Erysipelas has the characteristics of a specific infectious disease with a constant cause, lesions of the same character and a definite clinical course; yet

presumably the same streptococcus which causes the erysipelas produces in the lungs, or in the uterus, or in the peritoneum, a totally different process.

**NATURAL IMMUNITY.** It has been known and experimentally demonstrated that certain animal species are immune or resistant to the action of organisms to which other animals, and even species closely related, are susceptible. Under natural conditions the mode of life may not favor infection, which seems to be the cause for the infrequency of tuberculosis in susceptible animals in a feral state. The immunity may depend upon peculiarities of anatomical structure which offer a passive resistance to infection. Apart from such considerations under the most favorable conditions for infection the disease may not be acquired. This is due to the fact that in the body of the animal, resistant and bacterial destructive substances are either already present or easily formed. It has been found that phagocytic destruction of bacteria more easily takes place in the resistant animal. There may be a high degree of natural resistance to the action of bacterial toxins, due either to the presence of a neutralizing antitoxic substance in the blood, or to the fact that the toxin is not able to act on the cells, or the toxin may have a special affinity for the cells of some non-essential tissue. The toxin immunity may not be absolute. The horse has the greatest susceptibility to the action of tetanus toxin. If the minimal fatal dose for one gram of horse weight be taken as a unit, the scale of resistance for some other animals is as follows: for 1 gram of guinea pig, 2 units are fatal; 1 gram of goat, 4 units; 1 gram of mouse, 13 units; 1 gram of rabbit, 2000 units; 1 gram of chicken, 200,000 units.

**SUSCEPTIBILITY.** Variations in individual susceptibility are difficult to estimate. The fact that certain individuals in epidemics, in spite of apparent exposure to infection, do not acquire the disease may be in large degree due to accident. There is no immunity of tissues to the action of bullets and yet most soldiers go through battle untouched. Immunity may have been acquired by previous infections which were not recognized. It is even not inconceivable that immunity may be acquired by an infection which does not become evident, immunity being developed during the stage of incubation and before constitutional disturbance appeared. The resistance of individuals may be lowered in a

variety of ways. Experimentally, it has been shown that hunger, extreme fatigue, prolonged narcosis, refrigeration, will increase animal susceptibility, and in man famine and pestilence go hand in hand. A previous disease may render infection more probable. This is seen not only in the secondary infections, but in the frequency with which infectious diseases follow one another. The very ill understood condition of taking cold, or refrigeration, makes infection more probable, and chronic alcoholism increases both the frequency and severity of certain infections such as pneumonia. All of these conditions may, in various ways, so affect the nutrition and vitality of the cells that they no longer react with the same energy. Age has an influence on infection. Certain diseases are known as the diseases of childhood and it is assumed that this is because of greater susceptibility on the part of the young. Children, however, represent raw material without immunity conferred by previous attacks. In the pre-vaccination period, smallpox was preëminently a disease of childhood although all ages probably are equally susceptible. The period at which children are most susceptible to infectious disease is during the school age when the close association gives better opportunity for infection. Children are more susceptible to secondary infections, particularly those caused by streptococci, than are adults. This is shown by the frequency of broncho-pneumonia and otitis media. They also are more susceptible to infections of the alimentary canal. It is uncertain whether this depends upon conditions favoring the entry of organisms or upon absence of the general mode of defense.

THE INTERACTION BETWEEN THE TISSUES AND THE INFECTING ORGANISMS is well shown in staphylococcus infection. When the cornea of a rabbit is inoculated with a culture of staphylococcus aureus, the organisms grow in the cell spaces of the tissue forming masses conforming to these, the entire mass of organisms being compact. The vessels of the surrounding conjunctiva and the scleral vessels at the edge of the cornea become congested; emigration of polynuclear leucocytes takes place rapidly and the emigrated cells pass through the tissue forming a compact wall around the bacteria, not only the cell spaces but the interfibrillar tissue also being filled with them. This wall of leucocytes, however, is not formed immediately around the masses of bacteria, but an area of completely necrotic tissue intervenes between the bacteria

and the leucocytes. The advance of the leucocytes is halted at a distance from the masses of cocci. Not only is their progress halted, but the necrosis which has taken place in the corneal tissue extends, to some extent, to the leucocytes. Such a wall of leucocytes in itself forms a protection in limiting the advance of the bacteria and probably in limiting and opposing the action of the destructive substances which they produce. The next process is the liquefaction of the tissue around the bacteria and the advance of the leucocytes. The liquefaction of the tissue is due to proteolytic ferments, the production of which is a property especially marked in the pus producing bacteria. In the cornea the liquefaction and leucocytic advance go together; in other tissues the leucocytes gain resistance to the necrotic or paralyzing action of the bacterial substances, and advance before the histolysis of the necrotic tissue takes place. The formation of this definite circumscribed wall of necrotic tissue which at first forms a bar to the leucocytes is one of the most striking features of abscess formation. When staphylococci are injected into the ear vein of a rabbit, the cocci find lodgment within the vessels at various places, particularly in the heart and the kidneys. They multiply, form masses occluding the vessels, and around each mass the same process takes place as in the cornea. There is no immediate phagocytosis, but before this takes place there is either a neutralization or destruction of the necrotizing substance or the action of opsonins on the bacteria stimulating phagocytosis, or both. With the histolysis of the tissue an ulcer is produced on the cornea; an abscess, when the process is within the tissues. Destruction of cocci both by phagocytosis and bacteriolysis proceeds rapidly. The healing of both the ulcer and the abscess is brought about by the formation of granulation tissue.

The production of necrosis of tissue around bacteria is not a common property. Masses of typhoid and other bacteria may be found in the tissue without necrosis, nor is leucocytic reaction always present. In general, however, the lesions associated with the presence of bacteria in the tissue are of inflammatory character. In certain cases the tissue reactions are so characteristic and so specific that from them the nature of the infection can, with great but not absolute certainty, be determined. The tissue reaction characteristic of a special organism does not, however, always take

place. The tubercle is one of the most characteristic of the products of bacterial action, but the tubercle bacilli may, in certain cases, produce suppuration or fibrino-purulent exudation.

**ATRIUM OF INFECTION.** Bacteria usually produce a local lesion at the point of entry which is called the infection atrium. From this they may extend further into the body by means of the lymphatics or by the blood, producing metastases. The situation of the metastases is determined by many factors, the most important of which probably are the varying degrees of resistance in the different organs of the body. Certain organs have a high degree of resistance to bacterial action in general as the tissue of the brain, the muscle, the testicle and the ovary. The presence of metastases in certain organs may be determined by the character of the organism; for example, the metastases in the muscles and testicle in glanders, the bacillus mallei apparently finding in these organs the most suitable environment for multiplication. The blood must be regarded as a resistant organ. In every infection it is probable that organisms enter the blood by means of the lymphatics, some organisms passing through the barriers of the lymph nodes, or by means of blood vessels with or without a preceding formation of thrombi. The entering organisms may be destroyed in the blood, or this may act simply as a carrier by means of which the organisms are deposited in other places; in still other cases the organisms may survive or even grow in the blood, the condition being known as bacteræmia. The best example of bacteræmia is seen in anthrax or in pneumococcus infection in highly susceptible animals.

**CHRONIC INFECTIONS.** Infections by some organisms tend to pursue a chronic course. Tuberculosis and leprosy may be taken as the types of such chronic diseases. In the case of tuberculosis the bacillus is of slight virulence and ordinarily of little power of growth in the body. The lesions produced as a rule are circumscribed and extend slowly by infection of adjacent tissue. The formation of connective tissue is stimulated and the areas of disease may become surrounded by dense capsules of connective tissue which act as a protection against further advance. The organisms persist in the areas and further infections occur at intervals. In other chronic infections the organisms may collect in certain organs, as in the spleen, and from these depots further invasion occurs. Each onset may be met by the creation of a

temporary general immunity which does not extend to the destruction of the organisms in the isolated depots. In the acute infections, on the other hand, the resistance of the body increases to an extent which brings about destruction of the infecting organisms, resulting in recovery or death from the inadequacy of resistance.

**PERIODS OF INFECTIOUS DISEASE.** In many of the infectious diseases there is a period between the attack of the organism and the appearance of constitutional evidence of the disease which is called the *period of incubation*. It is variable in the different infections and may vary in different cases of the same infection. In certain infections, as in smallpox, it is dated from the opportunity for infection, and the disease appears almost invariably twelve days after this. In certain cases the period is terminated gradually, the constitutional symptoms slowly appearing; and in others, the best example being smallpox, the termination is sudden. Nothing in the infectious diseases is so uncertain as our knowledge of what is taking place during the period of incubation. In those infections in which there is a well-marked infectious atrium or primary lesion, it seems evident that during this period the organisms are multiplying and producing toxins in the focal infection, and the constitutional disturbances begin when a sufficient amount of toxin has been produced. The defensive forces of the blood may at first be sufficient to neutralize toxins and to destroy bacteria; the constitutional disturbance appears when the defenses of the body are overcome. It is not even necessary that there should be a local infection, for the bacteria may find opportunity for growth on some one of the surfaces and there produce the toxic substances, the absorption of which produces the constitutional disturbance. In smallpox, in scarlet fever and in typhoid fever no such primary infections have been found. In most infections, there follows the period of incubation, a period in which the signs and symptoms of the disease develop, the period of *invasion*. The symptoms may develop rapidly, frank invasion, or insidiously. The acme of the disease or *fastigium* may be slowly or rapidly attained. This is followed by *deservescence* or decline which may take place rapidly (*crisis*) or slowly (*lysis*). The period of *convalescence*, during which the patient returns to a normal state, follows the decline. These conditions are best seen in the acute infectious diseases, such as pneumonia and typhoid fever.

**RECOVERY** takes place when the body has acquired the power of destroying the organisms and neutralizing their toxins. When in diphtheria the toxins are neutralized by the antitoxins, not only is the toxic action on internal organs prevented, but the concentrated toxins associated with the bacilli on the mucous surface are no longer able to produce the epithelial necrosis and fibrinous exudation which give the best conditions for bacterial growth. The bacteria can exist for a long time as saprophytes on the mucous surface, but no longer are capable of injury. The bacteria which invade the body are destroyed both by phagocytosis and by bacteriolysis. In any case recovery from an infection means that the body is immune to the action of the infecting organism. In certain cases the immunity is local only, as in staphylococcus infection; infection in a locality adjacent to the focus which has become immune to the organism can take place, as is seen in the frequent new infections around a furuncle. In this case there has been no general invasion of the body resulting in a general increase of defensive powers, but both the attack by the bacteria and the defense by phagocytosis, chiefly have been local. The general immunity always lasts for a period which, in some infections, extends through the life of the individual. Such immunity depends upon the cells retaining the power, on the reception of the specific stimuli, of producing specific antibodies. The exercise of definite functions by the cells increases the facility of performance.

**REMOVAL OF ORGANISMS.** Bacteria are discharged from the infected individuals not only when lesions communicate with surfaces, but they may be discharged through secretory channels. In typhoid fever the bacilli are discharged by the urine and bile, in hydrophobia the virus (of an unknown nature) through the salivary glands; cholera and dysentery organisms when injected into the blood appear in the alimentary canal. This is not a process of secretion; the bacilli produce small lesions in the tissue by which they enter the ducts and are conveyed into the urine and bile in which places they find opportunities for growth. They may persist in the cavities for some time and, in the case of the gall bladder, for years after the disease is recovered from causing the affected individuals to act as "carriers."

**HEREDITARY.** Hereditary transmission of infectious disease cannot occur, for the factors in heredity are concerned with germ

plasm; an infectious organism, if present, would be a case of germ cell infection and not of hereditary transmission. The ova can become infected and the infection extend to the embryo, but infection of the spermatozoön, if it occurs at all, must be very infrequent. Germinal infection of the ova occurs in insects, particularly in ticks, but it is uncertain that it ever occurs in man.

**INTRA-UTERINE INFECTION.** Infection of the embryo or fetus by the mother, by way of the placenta, has been demonstrated experimentally, and in man has been shown in syphilis, in typhoid fever, in tuberculosis and in small-pox. It may take place either with or without the production of a focus of infection in the placenta. In certain cases no lesions of the placenta have been found, but to disprove the existence of minute lesions would be well nigh impossible. The presence in the placenta of foci of necrosis, which is very common, would favor infection by giving bacteria places for growth where they would be removed from the action of the blood.

**SECONDARY INFECTION,** that is, an infection by an organism different from that producing the primary infection, plays an important part in the infectious diseases. The secondary organism may find entrance into the body through lesions produced in the primary disease, as in the case of infection by streptococci through the areas of ulceration in the lungs produced by the tubercle bacilli. The resisting powers of the body may be so weakened in the first infection that the secondary infection may be but little opposed. By the indefinite term of weakening of resistance must be understood in a general way an inability of the body to produce those substances on which immunity and resistance depend. The bone marrow may share in the general injury produced by the first infection and not only phagocytosis, but the reactive leucocytosis be inhibited. In some of the most typical of the infectious diseases death, in most cases, is to be attributed not to the primary cause, but to the secondary infection. The streptococcus is the most common organism of secondary infection, and the lungs the most frequent atrium of infection.

**TERMINAL INFECTIONS** are infections which occur shortly before death. Cultures from organs at autopsies frequently show various pathogenic organisms in the blood or in organs where they could only be carried by the blood circulation. There may be no lesions



in the tissues associated with the organisms, or lesions of slight development.

**VARIATIONS IN INFECTIONS.** The great differences which infections show in severity, in character and extent of lesions and of distribution in the body, depend upon a number of factors. In the infection there is an interaction of two organisms and the enormous variability of living matter in such an interaction would of itself produce differences in result. However nearly the same conditions can be approached in experimental infections, the result is not always the same. If susceptible animals of the same litter and weight be inoculated with an infectious organism which has been shown to be fatal for the species, the interval before death varies and if a less virulent organism be used some of the animals will die, some recover and in some there may be little or no result. In this experiment the conditions on the side of the infecting organisms are uniform for it may be assumed that in the large number of organisms used for inoculation and taken from the same culture, average conditions will be found. In the natural infections the differences are more marked because more factors enter. There may here be differences due to variations in virulence of the infecting organism and in the number which enter, and on the part of the body variations in the general resistance and in the resistance of the particular tissue or organ affected. Different cultures of the same organism vary in their power to produce disease in animals. The infectious power or pathogenicity can be increased by passing the organism through the more susceptible animals or by growing them in collodion sacs placed in cavities in the animals so that the growing organisms come in contact with the tissue fluids; it can be diminished by constant growth in the test tube, by action of light, by variations in temperature, by the action of chemical substances. Virulence in an organism depends upon two factors, the power of growth and the power to produce toxic substances, the two conditions sometimes, but not always, acting together. The organism growing within the body acquires immunity to the inhospitable activities of the host, and may transmit the acquired immunity to successive generations in the same way that the cells of the host acquire immunity and transmit it to successive generations of cells. In the same disease, as in tuberculosis, we find in one case great numbers of bacilli which produce

little reaction in the tissues about them, and in another case extensive tissue lesions associated with small numbers of organisms. The leprosy bacilli have, at times certainly, enormous power of growth and produce, in relation to their numbers, lesions of slight extent, while the tetanus bacilli have but feeble power of growth but great toxicity. In experimental infections quantity or doses of organisms required to produce infection vary with different species and with different strains. Certain organisms are so highly infectious that a single individual may infect an extremely susceptible animal, as anthrax in mice; but in general greater numbers are required. How much the number of organisms entering the body influence infections in man is uncertain.

## THE SPECIAL INFECTIONS

It would be possible to make a classification of the infections according to the type of tissue lesions produced in each, but the action of the bacteria varies so much, is affected by so many conditions, that such a classification is artificial. Suppuration, for instance, is most frequently produced by the pyogenic bacteria, but a number of organisms, which ordinarily exert a toxic action, or which produce lesions of the character of tubercles, may, under conditions which are imperfectly understood, produce typical suppuration, and the pyogenic cocci may not act in the way usual for them.

## STAPHYLOCOCCUS AUREUS

This is a coccus which, both in cultures and in the tissues, tends to occur in clumps and masses. It grows on all of the usual laboratory media and produces a golden-yellow pigment. It is widely distributed and the ease with which it grows and the wide temperature limits of growth,  $10^{\circ}$  to  $40^{\circ}$  C., makes saprophytic growth possible. There is an endotoxin combined with the bodies of the cocci and growing in cultures it produces a hemolysin and leucocidin. It also produces a proteolytic ferment and liquefies gelatine. The virulence of different strains of the organism varies greatly and the virulence is increased by passage through animals.

The susceptibility of animals to infection by this organism varies greatly both as to species and individuals, and on the whole they seem less susceptible than man. Of the common laboratory animals rabbits are the most susceptible. Infection by the staphylococcus is greatly favored by the presence of a focus in which the organisms can grow removed from the action of the tissue fluids and where they are prevented from passing into the blood. Injection of a bouillon culture of the organisms into the peritoneal cavity of a dog may produce no effect, but if a portion of potato or agar culture is placed in the cavity peritonitis results.

The staphylococcus is the typical pyogenic organism. Circumscribed abscesses in the tissue are more often produced by this than by any other organism. The first effect of the organism is the production of an area of necrosis in the tissue surrounding it. It has a marked positive chemotaxis for the polynuclear leucocytes and, by means of the proteolytic ferment which it produces, the intercellular substances are dissolved and a cavity formed in the tissue containing leucocytes, cell and tissue detritus, and organisms. The wall of the cavity is filled with leucocytes and a dense granulation tissue is formed. This is the pyogenic membrane from which leucocytes continually pass into the cavity. The tension of the pus in the cavity may exceed the tension in the surrounding tissue. The abscess may extend to a surface, by the continuance of the tissue liquefaction aided by the tension of the contents, and dis-

charge. On the surface of the body this is favorable, but if the discharge of the abscess into a body cavity takes place, the infection extends to this. Healing takes place by the destruction of the organisms by phagocytosis and the tissue loss is made good by the usual processes of repair and regeneration. Local immunity, due to a local defense by phagocytosis and adaptation of tissue to toxic action or the greater resistance of the granulation tissue which replaces the parenchyma, may be produced without any general immunity. The greater the virulence of the organism the less may be the local reaction. A general leucocytosis is a part of the infection. There is less tendency for the extension of the infection by means of lymphatics and blood than in the case of the streptococcus infections. In the formation of the abscess but little fibrin is formed and this undergoes liquefaction. When the infection of a serous surface results the exudation may contain large amounts of fibrin.

**PRINCIPAL LESIONS PRODUCED.** Furuncle and carbuncle: A furuncle is a local necrosis and suppuration of the corium due to infection of a hair follicle. The organism grows in the contents of the follicle and produces necrosis, which extends with the multiplication of the cocci. The dense tissue of the corium is resistant to liquefaction and the necrotic tissue forms a hard mass, the so-called core of the furuncle. In the carbuncle the necrosis is more extensive and may involve the subcutaneous tissue and fascia and several openings may appear in the skin over the area. The condition is the same in furuncle and carbuncle.

Acute osteomyelitis is most frequently due to the staphylococcus. This is an infection of the marrow of the long bones often combined with infection of the periosteum. Necrosis, purulent exudation and softening is produced in the marrow and the necrosis is extended, particularly when the infection involves the periosteum, by closure of the nutrient vessels of the bone. Large areas of necrotic bone, *sequestra*, are formed which become gradually enclosed by a formation of new bone called *involucrum*. The organisms may persist for months or years in the necrotic tissue and from this source extensions of the infection take place from time to time. The primary infection of the bone takes place from the blood and may be secondary to some acute disease or there may be no ascertainable focus of primary infection. The process is

much the same as in a furuncle, the difference being due to the nature of the tissue affected.

Acute meningitis, produced by the staphylococcus and resulting in a fibrino-purulent exudation in the pia-arachnoid, is almost always secondary to some localized infection in the brain or in the adjoining tissue.

Acute peritonitis, pleuritis and pericarditis may be produced, usually, by extension of infection from an adjoining focus. The exudation in the beginning is fibrino-purulent and the longer the process lasts the more purulent does the exudation become.

Acute endocarditis is frequently caused by the staphylococcus and the disease tends to assume the ulcerative form with destruction of valves, and extension into the myocardium.

Infection of the blood may take place from any primary lesions, resulting in numerous metastatic abscesses in various parts of the body. In these cases the metastases are often the result of emboli coming from infected thrombi. These small emboli carry the organisms and the associated toxic substances, and to the effect of these is added the vascular occlusion and necrosis of tissue resulting from this.

Degenerative lesions in the internal organs are common in fatal cases of infection produced by this organism. Amyloid degeneration often follows chronic osteomyelitis.

#### A CASE OF LOCAL AND GENERAL INFECTION WITH THE STAPHYLOCOCCUS AUREUS

**Anatomical Diagnoses.** Staphylococcus aureus septicæmia; Subcutaneous abscesses; Multiple abscesses in lungs and kidneys; Congestion of lungs; Slight acute swelling of spleen; Acute fibrinous pleuritis; Chronic adhesive pleuritis; Chronic mitral endocarditis; Infarction of lung; Healed tuberculosis of mesenteric lymph node.

Male, white, age ten years. He complained on October 27th of pain in both legs below the knees. Up to this time he had been perfectly well. Following the pain in the knees, fever and some rigidity of the muscles of the neck developed and diagnosis of cerebrospinal meningitis was made. On examination when admitted to hospital November 3rd, there was no evidence of meningitis save the rigidity of the neck muscles. On both legs below knees there were tender blue discolorations. Tem-

perature 103. Delirious. Died without developing further signs a few hours after entering hospital.

Autopsy, November 4th, twelve hours post mortem. Body that of a well-developed and fairly well-nourished boy. Rigor mortis present. Marked lividity over dependent portions of body and sides of neck. There is purple discoloration over the anterior surfaces of both legs, especially marked on the right side just below the inner side of the knee joint. There is a similar area on the left side of the lower jaw. There are no petechiæ. On incising the areas of discoloration on the legs there are foci of pus in the subcutaneous tissues and considerable turbid serum. This condition is more marked on the right leg. The knee joints and bones of the legs are normal.

Subcutaneous fat over body in fair amounts. Muscles well developed. The peritoneum smooth, free from adhesions. There is a firm, rather nodular lymph node, 2 cm. in diameter, near the root of the mesentery and nearest to the duodenum. On section the contents are dry, gritty and caseous with a distinct peripheral capsule. The other mesenteric lymph nodes are normal.

Pleural cavities. A few old, firm adhesions over the right upper lobe, and a fibrinous exudate over the lower and basal portions of the right lower lobe. This is easily stripped from the surface and is of a yellow granular appearance. On the left side the lobes are adherent to each other by thin fibrous adhesions.

Pericardium and cavity normal.

Heart, weight, 130 grams. Epicardium normal. There is little sub-epicardial fat. The myocardium is pale, of a light chocolate-brown tinge especially near the papillary muscles. Consistency normal. There is slight thickening along the free edge of the anterior curtain of the mitral valve close to the attachment of the chordæ tendineæ. There is also a small firmly attached wart-like vegetation on this valve. The other valves of the heart are normal.

Lungs. The lower lobe of right lung is of a dark red color in dependent portions and has scattered over its surface a few discrete round areas from 2 to 5 mm. in diameter. On palpation these are firm and on section there is an area of purulent softening in the center. Others contain in the centre a small amount of pus with intense congestion and hæmorrhage in the periphery. The intervening lung tissue is hyperæmic. A few small miliary abscesses in the middle and upper lobe. Left lung contains a few miliary abscesses. On the posterior surface of the lower lobe there is an area approximately 5 by 4 cm., which is firm, deep dark red in color and over which the pleural surface has lost its luster. On section the area is solid and extends 5 cm. into the lung tissue and is sharply circumscribed. The bronchi contain thick viscid blood-stained mucus.

Spleen, weight, 95 grams. Capsule is smooth. On section soft, follicles distinct. Pulp easily separated, color dark red.

Pancreas normal.

Stomach and intestines normal.

Liver, weight, 1010 grams. Capsule smooth, color dark chocolate brown. Lobular markings distinct, consistency normal. A general fine yellow mottling throughout.

Kidneys, weight, 195 grams. Of equal size. Cortex slightly swollen. Capsule strips readily leaving a smooth pale surface on which the stellate veins are prominent. On section a few scattered miliary abscesses are seen varying in size from 1 to 3 mm., generally situated in the cortex and circular in outline.

Adrenals, genitalia, aorta and organs of neck are normal.

Brain, weight, 1420 grams. Calvarium and meninges normal. Surface and sections of brain are all normal.

Middle ears and mastoids normal.

Cultures from blood and from abscesses all show pure and abundant growth of staphylococcus aureus.

**REMARKS.** The case is that of an acute infection with the staphylococcus aureus, the source of infection being not ascertained. This is not uncommon, a slight lesion on the surface may be overlooked, or may have healed and no recognizable trace remain and the organism, after existing for a time in some internal focus, may have suddenly invaded the blood and produced the metastases. In these conditions the organism is usually one of great virulence. Both the clinical and autopsy findings show that the subcutaneous abscesses below knees were the oldest of the metastatic abscesses. The bi-symmetry of these is probably accidental. The purple color of the skin over them, due to intense congestion with hæmorrhage, led to the thought of purpura on the first inspection of the body and the note "no ecchymoses" indicates the thought and the exclusion. The abscesses in the lungs and kidneys are due to hæmotogenous infection. Note the varying size of those in lung which indicates differences in time of infection. In the lung there is also an area of congestion, hæmorrhage and necrosis described as an infarction. No thrombus as the source of the embolus which produced the infarction was seen, but there was almost surely thrombosis in some of the small veins adjoining the subcutaneous abscesses which gave origin to the emboli. There is a slight acute



swelling of the spleen due to acute congestion. Meningitis was suggested clinically from the delirium and the rigidity of neck muscles. These symptoms were due to the effect on the brain of the toxic condition of the blood.

There had been two, and possibly more, previous infections. The evidence in the mitral valve of a previous acute endocarditis which had healed leaving a valve slightly thickened with a small mass of organized tissue upon it but functioning perfectly. A fresh staphylococcus infection at this point could easily have taken place. The caseous and calcareous mesenteric lymph node is evidence of a previous infection with tubercle bacilli from the intestinal canal. Without the demonstration of tubercle bacilli either microscopically or by animal inoculation this cannot be regarded as certain, but the relation of a caseous and partly calcified lymph node to tuberculosis is almost sure. This old tuberculous infection took place from the alimentary canal. The old pleuritic adhesions may have been due to infection of the pleura which occurred at the time of the endocarditis on to an independent infection.

## STREPTOCOCCUS PYOGENES

Streptococci divide in one dimension of space, the individuals adhering and forming chains. There is considerable variation in the length of the chains. The streptococci form on solid media minute dew-like colonies; in bouillon, the growth is more rapid and they form long tortuous chains which have a tendency to adhere, forming flakes in the medium. Gelatine is not liquefied. In cultures most streptococci produce a hæmolysin, but it has not been possible to explain at all the pathogenic action of the organisms by such toxic products as can be isolated from them. The optimum culture temperature is  $37\frac{1}{2}$  degrees; at room temperature the growth is feeble, the cultures lose their virulence and easily die.

In no pathogenic organisms is there so much variation in virulence. Some have no virulence, in others the virulence is feeble and in others the virulence is so great that the body seems utterly devoid of resistance and the organisms produce but little leucocytic reaction. Of the laboratory animals white mice and rabbits are the most susceptible to infection.

The streptococci may produce typical suppuratation and abscess in the tissue. As a general rule the foci of infection are less circumscribed than those produced by the staphylococci, there is more surrounding oedema and a greater tendency for the infection to extend by the lymphatics. Secondary infection is more frequently produced by the streptococci than by other organisms.

Primary and especially secondary infections frequently take place from the mouth. Streptococci are so commonly found in the mouth that they can almost be considered normal inhabitants, and in case the normal resistance of the tissues is diminished, infections of the lungs by way of the bronchi or of the middle ears by extension along the Eustachian tubes easily results. So common is the streptococcus infection of the middle ear in children under one year of age that it is a frequent finding at autopsies, and the same may be said of streptococcus broncho-pneumonia. Of the primary infections in the mouth the most frequent is acute tonsillitis, the entry of the organisms taking place from the crypts.

The organism is also a frequent cause of acute endocarditis and inflammations of the serous membranes. The exudate in the latter is rarely abundant and contains but little fibrin, and the vascular reactions are but little marked. It also is the organism most frequently concerned in the post partum infections of the uterus; the infection takes place usually at the placental site and a diffuse suppurative inflammation with extensive necrosis is produced. The infection may extend to the parametrium by way of the lymphatics and thence into the peritoneum. The blood usually is infected, but metastatic abscesses do not so frequently result as in staphylococcus infection. Notwithstanding the fact that there is but little evidence of toxin production by the streptococci in cultures, there is marked constitutional disturbance in the infections and the internal organs show evidences of the action of toxins. Focal necrosis of the liver and acute glomerular nephropathy is frequent.

The streptococci are the cause of an acute inflammation of the skin which is called erysipelas. The infection is in the corium, there is intense redness and swelling of the skin which gradually extends over the surface and which is most marked at the line of extension. The exudation is serous or sero-purulent and may extend through the epithelium, lifting up the horny layer in the form of blebs. The streptococci are found in the lymphatics of the corium and chiefly at the advancing edge. The subcutaneous tissue may become infected, a diffuse phlegmonous inflammation with much necrosis resulting. No demonstrable specificity is attached to the organism which produces erysipelas; infection from this source is not characterized by any peculiar features.

#### A CASE OF STREPTOCOCCUS INFECTION OF THE UTERUS PROBABLY FOLLOWING ABORTION

**Anatomical Diagnoses.** Acute septic endometritis of puerperal uterus; Acute purulent metritis; Acute fibrinous pleuritis; Empyema of left side; Bilateral hæmatogenous abscesses of lungs; Acute splenic tumor; Acute glomerular nephropathy; Laceration and erosion of external os uteri.

Female, white, age thirty-six years. The patient came into the hospital in evening in semi-moribund condition with signs of pleural effusion

on left side. Died the next morning without being at any time fully conscious.

Body that of a well developed and well nourished female. Rigor mortis in extremities. Surface normal. Both breasts enlarged. On section of mammary glands a whitish opaque material exudes and on pressure the same can be expressed from the nipples. Abdominal fat abundant, pale, yellow. Muscles red.

Peritoneum. The large intestine greatly distended with gas. Mesenteric lymph nodes not enlarged. The spleen shows a few soft fibrinous adhesions on the surface.

The left pleural cavity contains 600 c.c. of reddish-grey turbid fluid containing fibrin. The lung is collapsed, its pleural surface covered with a fairly firm fibrino-purulent exudation over an intensely congested lung surface. Over the pleura of the right lung there is a patch of exudate on the posterior portion of the lower lobe similar to that over the left lung. The pericardium and heart normal.

Lungs. The left lung small, compressed. The lower lobe on section is granular and nodular. In one of the larger foci of consolidation there is a cavity 1 cm. in diameter filled with thin purulent material. Similar nodules are found in the lower lobe of the right lung.

Liver of ordinary size, the consistency normal.

Spleen large, its capsule tense, showing a few soft fibrinous tags. On section, pulp bulges at edges, is soft and grey-red in color. Follicles large.

Both kidneys are alike. The capsule strips easily, leaving a smooth, pink-gray surface on which the stellate veins are very prominent. On section the cortex is pale, increased in size, bulges slightly at cut edges. The markings are obscure. The glomeruli are visible as pale sand-like glistening bodies the size of pin points. The vessels of pyramids injected.

Adrenals, pancreas, gastro-intestinal tract normal.

Genito-urinary tract. The uterus is enlarged, the parametrium is smooth and shiny except on left side where the ovary is adherent. The external os measures 2 cm. transversely. Its edges are ragged and torn, the lips smooth, everted, showing dark brownish erosions on the mucosa. The wall of the uterus is thickened, averaging 3 cm. The sinuses are easily seen. The cavity of the uterus is regularly enlarged, the endometrium of a dark brown color. On the anterior surface there is an irregular ragged necrotic mass. On section of the uterus beneath this the wall is distinctly softened and pus can be squeezed from the cut surface. In the region of the cervix there is a cavity in the wall 1 cm. in diameter filled with purulent material, and smaller cavities are throughout the

lower part of the uterus. In the left ovary which is adherent to the uterus there is a large corpus luteum. Smears from uterus and pleural cavity showed abundant streptococci in short chains together with contaminating organisms seemingly of colon group. Cultures gave abundant growth of streptococci and colon bacilli.

Microscopic examination. Sections of lung showed numerous foci of purulent infiltration with masses of streptococci. The exudation on the pleura showed streptococci. The sections of kidney show characteristic lesions in the glomeruli consisting in occlusions of capillaries by cells of endothelial type with well marked degeneration of epithelium. The muscle fibres of the uterus large. Corresponding to the ulcerated area on the anterior surface of the endometrium there are necrotic masses with fibrin and blood. In the submucosa and muscularis are large areas infiltrated with polynuclear leucocytes. In the small vessels of the uterus in the vicinity of these there are fresh thrombi. Streptococci in large numbers are found in association with the lesions.

**REMARKS.** The case is one of pregnancy with delivery at about the eighth month. The case was regarded as one of induced abortion. Streptococcus infection of the uterus followed, the infection probably taking place at the placental site. An extension of the infection from the body of the uterus by means of the lymphatics to the parametrium followed, resulting in the circumscribed fibrinous inflammation involving the ovary in the fibrinous adhesions. There is also a focal infection of the peritoneum shown by the fresh fibrin on the spleen; infection of the blood took place probably through the uterine sinuses and following this the abscesses in the lung, the fresh fibrinous pleurisy and the empyema. All these lesions are due to the direct action of the organisms on the tissues. The acute glomerular nephropathy is due to the action of toxins.

#### A CASE OF STREPTOCOCCUS INFECTION OF THE MIDDLE EAR INVOLVING MASTOID WITH EXTENSION TO BRAIN

Anatomical Diagnoses. Acute otitis media; Necrosis and perforation of roof of middle ear; Acute purulent meningitis; Acute glomerular nephropathy; General parenchymatous degeneration; Focal necrosis of liver; Old healed tuberculosis of lungs; Streptococcus infection.

Female, white, twenty-seven years old. Body of medium size, poorly nourished, skin loose and dry. Pupils unequal. Immediately behind

left ear extending obliquely downwards and backwards from the mastoid process is an incision 6 cm. long with a large funnel-shaped excavation into the mastoid process. The wound is bathed in blood-tinged pus. With a probe, direct communication is found between the wound and the intracranial cavity. Subcutaneous fat is small in amount, muscle pale.

Peritoneum normal.

Pleuræ: Numerous dense adhesions at both apices posteriorly. Epicardium normal.

Heart 205 grams. Endocardium smooth. Coronaries normal.

Lungs. At both apices extending into the lung substance are numerous larger and smaller firm areas with puckering of the overlying pleural surface. On section the larger areas average 3 to 4 mm. Their centres are yellowish, dense and sometimes calcareous. Surrounding these larger areas are a few small hard miliary foci. The intervening lung substance is crepitant. Elsewhere the lungs are normal.

Liver, weight 1600 grams. The normal lobulation evident on surface and on section. Consistency fairly firm.

Spleen 190 grams. Soft, cut surface dark red. Trabeculæ and malpighian bodies visible. The pulp is soft, the capsule smooth, tense, but not thickened. Pancreas normal.

Kidneys, weight together 325 grams. Surface smooth, capsule easily stripped. On section, cortex smooth, somewhat enlarged and bulges above pyramids. The glomerulæ are visible, appearing as pale points. Pelvis and ureters normal. Adrenals normal.

Gastro-intestinal tract normal. Genitalia normal. The aorta for the most part smooth, but contains a few slightly elevated yellowish areas extending in the long axis.

Head and brain. Scalp strips readily from calvarium. On the left side of the skull practically the entire mastoid process has been removed. The dura is slightly injected. The pia arachnoid over left cerebral hemispheres shows numerous scattered areas of purulent infiltration, the areas of small size from  $\frac{1}{2}$  to 1 cm. and situated about the vessels. The cerebral surface of the tentorium is pale, smooth and free from exudation. Over the base of the cerebrum, particularly about pons and medulla, there is an abundant fibrino-purulent exudation. The cerebellar surface of the tentorium is bathed in pus and the entire surface of the cerebellum is thickly covered with fibrino-purulent exudation. At the base of the left temporal lobe there is a slightly softened area of cortex measuring  $1\frac{1}{2}$  cm. and infiltrated with blood. In the lateral ventricles there is a considerable amount of turbid opalescent fluid. Sections of brain show no lesions elsewhere. There is an opening 0.2 cm. in diameter

into the left middle ear through the tegmen tympani. On the edge of this opening the bone is necrotic and the opening corresponds to the area of softening in the temporal lobe. The left middle ear is filled with thick pus, the surface covered with granulation tissue. The drum is absent. The jugular vein is free from thrombi.

**Microscopic examination.** Lungs. Section through two of the caseous nodules show in the centre caseous necrotic masses surrounded by dense hyalin connective tissue with numerous lymphoid and plasma cells at the outer edge of this. Thick bands of the connective tissue radiate from the capsule into the surrounding lung tissue and the closely adjacent alveoli are collapsed. The small miliary foci are composed of nodules of connective tissue. A few giant cells on the edges of the caseous mass are seen. In the liver the sinusoids are distended with blood and contain numerous polynuclear leucocytes and endothelial cells. In numerous places about the central vein there are foci of necrosis. These are not everywhere present.

The spleen is deeply injected with numerous foci of hæmorrhage in the pulp. There are numerous polynuclear leucocytes throughout the pulp and mitotic figures occasionally are found in the endothelial cells of the sinuses.

The kidneys. There is very marked acute parenchymatous degeneration of the epithelium of the convoluted tubules. The cells are swollen and in the proximal tubules the swollen cells contain round hyalin masses. Similar masses are also found within the lumen. The glomeruli are large, swollen, the tufts entirely filling the capsule. There is a general increase in the cells, the capillaries contain numerous large cells of endothelial character and polynuclear leucocytes. The covering epithelium is in places swollen. In some of the capillaries of the glomeruli there are well defined fibrinous thrombi. Throughout the cortex there is considerable infiltration with polynuclear leucocytes, this particularly about the glomeruli.

The pia arachnoid covering the cerebrum and cerebellum is densely infiltrated with fibrino-purulent exudation. The vessels are dilated and migrating leucocytes are seen in their walls. In the exudation there are numerous large mononuclear cells, many of which contain polynuclear leucocytes. Streptococci are found in the exudate and within the cells. Smears and cultures from the exudation in the meninges gave streptococci. In the meninges the cultures were contaminated with other organisms. Cultures of the heart's blood showed a pure culture of streptococci.

**REMARKS.** The case is one of otitis media, due to streptococcus infection. The infection from the middle ear has extended into the mastoid cells. Necrosis of the bone has been produced and the infection has extended to the meninges and brain. Of the lesions in the organs, the most interesting and important is the acute glomerulo nephropathy. This is not an infrequent accompaniment of streptococcus infection. The diffuse character of the lesions in the kidney indicates that they are produced not by the bacteria acting directly on the tissue but by toxic substances. There is also in the case a slight degree of central necrosis in the liver.



**DIPLOCOCCUS PNEUMONLÆ (PNEUMOCOCCUS. DIPLO-  
COCCUS LANCEOLATUS)**

This is a coccus which in the body or in cultures occurs in pairs. The organism is elongated or lancet shaped, in pairs, rounded on the contiguous sides, the opposite ends bluntly pointed. The most characteristic morphological peculiarity is the capsule formation around the pairs of the organism. This always is found around organisms when growing in the blood and tissues and may be produced in cultures containing blood or animal fluids. The organism stains with the Gram stain. Growth in culture is not vigorous, appearing on solid media as minute dew-like colonies somewhat resembling streptococci but more transparent. Cultural conditions show that it is an exclusive parasite. No characteristic soluble toxin has been obtained. The toxic properties seem to be due to an endotoxine closely bound with the protoplasmic substance. Injection into animals gives varying results, mice and rabbits being the most susceptible. The virulence of the organisms derived from different sources varies greatly and the virulence is quickly lost in cultures.

In animals local lesions with abundant formation of fibrin may be produced or the organism enters into the blood and produces a fatal septicæmia. Not infrequently virulent cultures produce in rabbits hyalin thrombi in the glomeruli of the kidneys due to agglutination and fusion of the red blood corpuscles.

In man the organism is a frequent source of both primary and secondary infections. It is a frequent cause of otitis media and inflammation of the accessory sinuses of the nose, the infection taking place from the mucous surfaces where the organisms frequently are found in symbiosis. In addition acute endocarditis and acute inflammation of the serous surfaces and of the meninges may be due to primary hæmatogenous infection, the organism probably entering the blood from some concealed focus; or these infections can be secondary to some other focus of infection, the extension being by continuity or by the blood. Infection of the subcutaneous tissues, or infection of the parenchyma of organs

occurs more rarely. On serous surfaces the exudate usually contains large amounts of fibrin. The organism has been described as a cause of enteritis, and infection of the Fallopian tube may also occur. In very young infants infection of the blood very similar in character to the septicæmia produced in mice may take place. The focus of infection in these cases may be concealed and the blood contains great numbers of the organisms with well-marked capsules.

As the name of the organism implies, the lung is the most common site of infection in man. Acute croupous or lobar pneumonia in man is most generally associated with this organism. This is an acute inflammation of the lung which affects simultaneously lobes or large areas, and is characterized by an abundant exudation of fibrin, red corpuscles and leucocytes into the air spaces. Three well-defined stages of the lesions are distinguished. In the stage of *engorgement* the tissue is deep red, firmer than normal to the touch, but not solid and on section blood and fluid exudes. The tissue floats in water, but the submergence is greater than normal. Microscopically, there is intense congestion of the capillaries, the loops of which extend into the air spaces, and some serous exudation. This passes into the stage of *red hepatization* in which the tissue is solid, sections sink in water, and the redness is not so pronounced as in the previous stage. The cut surface is finely granular due to the projection of fibrin plugs from the alveoli and on scraping with a knife these are removed as granules. The tissue is seemingly more friable, the finger can be pushed into it, and sections break on bending. This is due to the solidification of the tissue preventing the distribution of the applied force over a larger area. Microscopically at this stage the congestion is no longer so marked and the alveoli are filled with exudate which consists of red corpuscles, leucocytes and fibrin. The relative amounts of the constituents of the exudation varies in different cases. There is usually some proliferation and desquamation of the alveolar epithelium. The third stage is that of *gray hepatization*. In this the red color gives place to a gray or grayish red. The solidification remains but the cut surface is smoother, more moist, and a turbid granular fluid is removed by scraping. Microscopic examination at this period shows the leucocytes relatively more abundant than in the early stage. The lymphatics both the subpleural and the central are

distended and filled with cells and fluid. A fourth stage *resolution* follows in favorable cases. In resolution the exudation undergoes autolysis by the action of proteolytic enzymes and is chiefly absorbed, although some passes out by the bronchi.

The entire lung may be involved and show the same stage of the disease, or lobes of both lungs may be affected and different stages may be found in different areas. The pleura always is involved and the exudate has the same character as in the alveoli; extension to the pericardium also is not infrequent. The internal organs do not present much evidence of toxic action, the spleen is but little enlarged and the parenchymatous degeneration of liver and kidneys is not marked.

Pneumococci are found in variable numbers and are both within the leucocytes and free. They are always more abundant in the earlier stages. In rare cases the condition of carnification of the lung, or chronic pneumonia, or organizing pneumonia supervenes on the acute. In this condition autolysis and absorption of the exudate does not take place and it becomes organized by the in growth of connective tissue from the walls of the alveoli and from the peribronchial connective tissue. The exudation in the interlobular septa undergoes the same fate. The lung in color and consistency approaches that of muscle. Microscopically, both alveoli and small bronchi are filled with vascular granulation tissue which later gives place to connective tissue. The process of organization is accompanied by thickening of the alveolar walls and abundant formation of elastic tissue. The process can involve entire lobes of the lung or appear in small foci. The lung so altered appears to be much less resistant to infection than the normal lung and both abscess and gangrene are not uncommon accompanying conditions.

In the acute infectious diseases of children focal infections of the lung with the diplococcus pneumoniae, the organisms entering and extending by the bronchi (broncho-pneumonia) and producing small areas of solidification, are common. It is certainly very remarkable that the same organism should produce in the one case so characteristic a lesion as lobar pneumonia and in the other small foci of infection not differing from the lesions produced by a number of organisms, and that there is so little tendency for both types to occur simultaneously. The peculiar action of the pneumococcus in producing

lobar pneumonia is very similar to that of the streptococcus in producing erysipelas. Nothing that we know of the organisms in either case gives a sufficient explanation.

#### A CASE OF PNEUMONIA

**Anatomical Diagnoses.** Acute croupous pneumonia of left lung with beginning resolution in upper lobe; Acute pleuritis on left side; Chronic adhesive pleuritis and peritonitis; Acute swelling of spleen; Acute otitis media; Fatty degeneration of intima of aorta; Congestion and acute degeneration of liver and kidneys.

White, male, aged twenty-two years. Entered hospital two days before death. Five days before entrance had a chill which was followed by continuous fever. Has now a slight cough, and complains of dyspnoea and pain in left side of chest on coughing and breathing. On examination the face is flushed, the pulse 100, temperature 103.5; lies on left side. There is dullness on percussion over the entire left lung extending posteriorly to axillary line, with bronchial breathing. Whispering voice more plainly heard and voice vibrations transmitted to hand on this side. A friction rub is heard in the axillary region. A blood count shows a leucocytosis of 45,000 with 89 per cent polynuclears. On the following day temperature remained elevated, the dullness and bronchial breathing increased, extending over the entire area of lung; the cyanosis is also increased. Death at 7 A.M. the following day.

Body that of a fairly well developed and fairly well nourished white male. Slight rigor mortis. No oedema.

Subcutaneous fat in fair amount. Muscles red and well developed.

Peritoneum. Smooth and normal save for adhesions between omentum and abdominal wall over a small area in the right iliac fossa and about the gall bladder. The liver somewhat depressed. Diaphragm on left side at sixth rib, on right at fifth interspace.

Pleural cavities. On the left side the visceral and parietal pleuræ are loosely united by delicate fibrinous adhesions. The pleural surfaces have lost their lustre and in part are covered with reticular masses of fibrin, in part the surface is granular and roughened. The exudate is easily removed from the visceral pleura, leaving an injected opaque surface. The parietal pleura can be stripped off in large sheets, which, observed by transmitted light, show deeply injected enlarged vessels, in the course of which small red areas, up to 2 mm. in diameter, are seen. In the right pleural cavity the surfaces in several places are united by fibrous bands most numerous over the lower lobe.

**Lungs.** The left lung is greatly increased in size, weight 1510 grams. The two lobes lightly united by fibrinous adhesions. Over the surface there are slight depressions corresponding to the ribs. The entire lung completely solidified save for a narrow area along the anterior edge of the upper lobe. Portions cut from various places sink in water. On section the upper lobe is pale grayish-red. The cut surface is moist and smooth. On scraping with knife, a thick viscid muco-purulent material is obtained, and on squeezing the tissue a similar fluid can be expressed from the cut bronchi. The color of the section is not homogeneous, in places more gray, in others redder. The line of demarkation between the solidified upper lobe and the air-containing edge is irregular. The section of the lower lobe shows complete consolidation, the cut surface redder than that of the upper lobe and more granular. On scraping this with the knife, small sand-like granules of irregular size are obtained. Both lungs are more friable, easily penetrated by the finger and on bending a slice of the tissue 1 cm. thick, it fractures, leaving a rough granular surface.

The right lung is smaller than the left and contains air throughout. The posterior part of the lower lobe is moist.

**Bronchial lymph nodes.** These are enlarged, contain a small amount of carbon pigment, on section are of opaque grayish-red color and are softer than normal.

**Pericardium.** Normal. A slight increase in the pericardial fat.

**Heart.** Weight 340 grams. The right side of the heart is dilated and contains a tough elastic clot, the upper surface of which is pale yellowish-white, the lower dark red. This clot extends as a branching mass into the pulmonary artery. The left heart contracted, valves and coronary arteries normal. Gastro-intestinal tract normal.

**Spleen.** Weight 320 grams. Capsule smooth, consistence soft, on section deep red, pulp easily pressed out, trabeculae and malpighian bodies obscure.

**Pancreas.** Normal.

**Liver.** Weight 1800 grams. Surface smooth, somewhat mottled and on section hyperæmic. Gall bladder small, contains a few cubic centimeters of bile.

**Kidneys.** Weight 295 grams. Capsule easily removed. Surface smooth. On section cortical markings visible, cortex more opaque, pyramids injected.

**Adrenals** normal.

**Bladder and genitalia** normal.

In the aorta there are a few small, not elevated, linear opacities, which are most marked in abdominal aorta, a few only being in the arch.

**Calvarium and dura** normal.

The longitudinal sinuses contain fluid blood and clots. Vessels of pia congested. Brain and cord normal.

Marrow of femur is almost replaced by red marrow. .

Right middle ear contains thick yellow pus, drum membrane not perforated.

Cover slips made from the lower lobe of the lungs show encapsulated diplococci in large numbers both within polynuclear cells and free. Cultures from the lungs, the blood, the spleen and kidneys give abundant pure cultures of pneumococci. From the ear a mixed culture of pneumococci and staphylococci is obtained.

**REMARKS.** The change in resonance, in sound conduction, and the transmission of sound vibrations to the chest wall are due to the changing of the lung from an elastic air cushion to a solid body. The increased number of polynuclear leucocytes in the blood is due to their greatly increased formation in the bone marrow, the number removed from the blood in the formation of the exudate being more than replaced. The red marrow in the shaft of the femur indicates the great hyperplasia of the blood-forming tissue. The intense congestion of an inflamed serous surface is shown in the stripped pleura. It is difficult to separate the normal pleura from the chest wall; in this case, the separation is facilitated by the greater saturation of the tissue with fluid. The exudate in the lung and on the pleural surface will be studied in the histological section. The spleen in this case is unusually enlarged. In most bacterial infections it is enlarged, the degree varying widely. The enlargement is due chiefly to congestion. The slight changes in the liver and kidneys are due to acute toxic degeneration. The inflammation of the middle ear is due to bacteria extending to this by means of the eustachian tube. The lines of fatty degeneration in the intima of the aorta are interesting as showing the relation which may exist between acute infectious disease and chronic arterio-sclerosis.

#### A CASE OF ORGANIZING PNEUMONIA FOLLOWING ACUTE WITH SECONDARY INFECTION OF THE MENINGES

**Anatomical Diagnoses.** Acute otitis media; Acute cerebrospinal meningitis; Acute pericarditis; Unresolved pneumonia; Acute pleurisy.

White, male, age two years. Body that of a fairly well developed, fairly well nourished male. Rigor mortis is present and complete;

there is a moderate amount of lividity most marked in the dependent parts. Skin is dry and smooth. External orifices are normal. Abdomen is considerably distended and tympanitic throughout. Pupils 7 mm. and equal.

**Peritoneal cavity.** The peritoneum is smooth and glistening. Cavity contains a normal amount of straw-colored fluid. Vermiform appendix is 10 cm. long; points upward behind the cæcum, to which it is closely attached; its mesentery is very short. Diaphragm reaches the fourth rib on the right, fourth interspace on the left side.

**Pleural cavities.** Right cavity is free from adhesions. The lower lateral aspect of this cavity has lost its lustre, has a distinct granular, ground-glass appearance, and its superficial blood vessels are injected. The left cavity shows numerous, moderately firm, fibrous adhesions which unite the lower lobe of the lung, in its lateral and posterior aspect, to the adjacent pleura.

**Pericardial cavity.** Pericardium is somewhat increased in size. The visceral layer is considerably thickened and has a distinct boggy feel. Upon opening the pericardial cavity 100 c.c. of a cloudy fluid escapes. In this fluid are numerous gray, fibrinous flakes. Both visceral and parietal layers of the pericardium are completely covered by a gray, elastic, rather dry exudate. Over the parietal layer of the pericardium this exudate averages about 2 to 3 mm. in thickness; over the visceral layer it is considerably thicker.

Heart not opened, preserved with attached pericardium for demonstration.

**Lungs.** Right: the lower lateral and posterior surface of the right lobe has lost its lustre; shows a distinct, granular, ground-glass appearance. No areas of consolidation are demonstrable in this lung. On section the lung is dark red in color, and from its surface a small amount of fluid blood escapes.

The upper lobe of left lung is hyperæmic. The lower lobe is firm and resistant. In places it is solid, of a yellow red color, not friable but tough. The solidified areas are not circumscribed but pass without outline into the tough but not solidified surrounding tissue. Pieces from the completely solid areas sink in water, those from other areas show a varying degree of submergence and all tissue from the lobe contains less than the normal amount of air. There is no regularity in the size or distribution of the solid areas.

**Spleen,** weight 65 grams. It is dark red in color. No pulp comes away upon scraping. The trabeculæ and malpighian bodies are distinctly visible.

**Liver,** weight 500 grams. On section it is of a uniform pale color. Gall bladder and ducts are normal.

Kidneys, weight 140 grams. Capsule strips easily leaving a smooth surface. Cortex bulges slightly beyond the capsule, and measures 6 mm. in thickness. The glomeruli are distinctly visible as fine glistening points. The pyramids are dark red; the pelves and ureters are normal.

Adrenals, pancreas, bladder, prostate and aorta normal.

Gastro-intestinal tract. The mucosa of the gastro-intestinal tract is normal. Mesenteric lymph nodes are slightly increased in size; on section are pale.

Head. Scalp and calvarium are normal. Dura is slightly adherent to the calvarium along the great longitudinal sinus, and strips easily from the underlying pia. The great longitudinal sinus contains a small amount of fluid and clotted blood. The pacchionian granulations are normal in amount and distribution. The brain shows a very marked and very extensive exudate in the pia arachnoid. This is most pronounced over the base and over the anterior half of each cerebral hemisphere. The convolutions are broad and flattened; the sulci are indistinct. In the anterior portion of the cerebrum, where the exudate is most pronounced, neither sulci nor convolutions can be made out as the exudate so completely obscures them. This exudate is most marked over the left hemisphere, about the fissure of Rolando and Sylvius, and over the left temporal lobe. The pons and medulla show a very marked yellowish exudate, generally similar in character to that covering the lateral hemispheres, although over the pons and medulla the exudate is more moist. This acute inflammatory process extends over the superior surface of the cerebellum and over its internal and lower aspect. The subpial vessels throughout the brain are deeply injected and stand out prominently. The brain substance is rather moist. The ventricles contain a considerable amount of cloudy fluid, in which numerous gray fibrinous flakes are visible. The surface of the ventricles is roughened and has a granular appearance. The sinuses at the base of the brain contain fluid and clotted blood.

Middle ears. Each middle ear contains a considerable amount of thick yellowish exudate.

Spinal cord. The fat about the dura shows marked injection of its vessels. Beneath the dura there is a large amount of cloudy fluid, similar to that seen within the ventricles, and the cord itself is covered with a yellow exudate similar in character to that seen over the lateral hemispheres.

Smears and cultures made from the cerebrospinal fluid, during life, showed the pneumococcus. Cultures made at autopsy from the surface of the brain, ventricles, middle ears, cord, pericardium, lungs (pneumonic area) and heart's blood showed the pneumococcus.



**REMARKS.** The condition began with an acute pneumonia in the lower lobe of the left lung. The pneumonia in this case did not resolve, that is, the exudate did not undergo autolysis but remained and became organized, and was replaced by connective tissue. The period of this primary infection cannot be ascertained. The pneumococcus infection persisted and has been followed by various extensions; to the middle ears on both sides, to the meninges, to the pericardium and to the pleura. Meningitis due to the pneumococcus is more common in children than in adults. It is difficult to say how infection extends to the meninges. It may extend by the blood, from the ears, or from the nasal sinuses.

#### A CASE OF ORGANIZING PNEUMONIA

**Anatomical Diagnoses.** Lobar pneumonia (left lung); Acute bilateral pleuritis; Organizing pneumonia (lower lobe, right); Acute splenic tumor; Hydropericardium; Arterio-sclerosis; Passive congestion of liver and kidneys; Chronic fibrous peritonitis; Acute otitis media; Congestion and oedema of brain; Cysts of choroid plexus.

White, male, age twenty-two years. Body fairly well developed, nutrition fair. Slight rigor mortis. No oedema. Subcutaneous fat in fair amount.

**Peritoneum.** Appendix 8 cm. long. Its mesentery extends to tip. Organ extends downward over the brim of pelvis. The great omentum is firmly adherent to abdominal wall over a small area in the right iliac fossa, to the right lateral parietal wall and to the gall bladder. Mesenteric lymph nodes are not increased in size.

Over both pleural surfaces there is a fibrinous exudate with uniting fibrinous bands. In the right pleural cavity in places, the fibrinous adhesions give place to delicate bands of connective tissue, this being most marked over the posterior aspect of the lower lobe.

**Pericardial cavity.** Shows slight increase, estimated at 75 c.c. of pericardial fluid.

Heart normal.

**Lungs.** The left lung does not contract on opening the chest. The two lobes are loosely adherent by fibrinous exudation. The lung, with the exception of a narrow area along the anterior border of the upper lobe, is completely solidified. The upper lobe of an opaque, gray white color, the lower redder, and this color distinction is fairly sharp. On section of upper lobe the surface of the section is smooth and moist and

on pressure a thick viscid fluid can be expressed. The surface of section of lower lobe is more granular and drier. There is normal crepitation along the anterior border of the upper lobe. The right lung, upper lobe, is congested, crepitant throughout, somewhat more moist on section than normal. The lower lobe, especially in lower half, is firmer than normal. On section it is generally firm, but there are areas which are tough and solid. These areas have an indefinite extension and vary in size. Portions of tissue from the centres sink in water. The solid tissue cannot be torn. In color these areas are distinguished from the surrounding congested lung tissue by a paler and more yellow color, in places the color is almost golden yellow.

Spleen. Weight 320 grams. Capsule smooth. Tissue of flabby consistency. Pulp soft, adheres to the knife and is of a deep red color. Neither trabeculæ nor follicles are visible.

Intestinal canal. Entire intestinal canal normal, also the abdominal organs save for congestion and cloudy swelling.

Brain. The pia arachnoid is congested and contains an excess of fluid. Easily stripped from convolutions. The brain moist. Some excess of fluid in the lateral ventricles; in the choroid plexus there are small cysts with clear contents.

Genito-urinary organs normal.

Intima shows a few yellow linear areas most marked in abdominal aorta, few being in the arch.

Right middle ear contains thick yellow pus.

Both cultures and cover slip preparations from the lungs gave diplococci for the most part, as shown in the smears, enclosed in polynuclear leucocytes, in culture morphologically conforming to pneumococci.

Microscopic examination of the solidified areas in the lower lobe of right lung showed within the alveoli masses of thick fibrin surrounded by connective tissue composed of cells and fibres. In places this almost filled the alveoli, only fragments of fibrin being present. These masses in places were attached to the alveolar walls projecting as polypi into the space. In other places they seemed to enter as a connected mass from the wall of terminal bronchus filling the entire series of spaces supplied by this. These plugs of connective tissue and fibrin contained blood vessels.

**REMARKS.** An initial acute croupous pneumonia of usual character in the lower lobe of the right lung. The exudate has in part undergone the usual resolution, in part, as in the solidified areas, it has remained and is undergoing organization. The conditions on which this depends are unknown. The date of this pri-

mary infection cannot be determined from the histological examination. This change, called *carnification* (from the resemblance of the tissue to muscle), may take place in the entire lobe which is affected, or in focal areas, as in this case. The infection of the left lung followed, the lesions being older in the upper lobe. The lesions in other organs dependent upon the lung lesions, congestion, etc., need no explanation. The peritoneal adhesions are evidently due to a slight infection of the peritoneum of remote date originating either from the appendix or gall bladder.

The small cysts of the choroid plexus which are described are frequently found and seem to have little or no importance in disturbing function.

#### A CASE OF ACUTE SALPINGITIS PRODUCED BY THE DIPLOCOCCUS PNEUMONÆ

The tubes with ovaries removed at operation and sent for examination. The patient a multipara, no lesions discoverable in vagina or uterus. The tubes are enlarged, the serous surface deeply injected and cloudy. The fimbriæ congested. On section the entire wall is thickened and oedematous, the lumen dilated and contains abundant, rather thick pus. On section all the vessels are dilated, there is mural accumulation of leucocytes and active emigration in the vessels of the mucous surface. The epithelium is retained and both this and the tissue beneath thickly infiltrated with polynuclear leucocytes. These are both between and within the epithelial cells. There is also considerable leucocytic infiltration beneath the serous surface. Characteristic diplococci pneumoniae were found in cultures and smears and on histological examination.

**REMARKS.** This case represents an unusual infection with this organism. Both the acute and the chronic forms of salpingitis usually are due to the gonococcus. Infection was most probably from the vagina and uterus although infection by the blood cannot be excluded.

## DIPLOCOCCUS INTRACELLULARIS MENINGITIDIS

This is a diplococcus of the same size as the gonococcus, appearing as two hemispheres separated by an unstained interval. It stains with any of the ordinary bacterial stains, but is decolorized by the Gram method. There is considerable variation in the size of the organism. It does not grow profusely on any of the culture media, but better on blood serum than on any other medium. On this it forms white, shining, viscid-looking colonies with sharply defined outlines. The organism may grow in bouillon or on various solid media, but the growth is feeble.

It has but feeble pathogenic properties when inoculated into animals. Cerebrospinal meningitis has been produced in goats and in monkeys by inoculating directly into the cerebrospinal meninges. The organism is an exclusive parasite. In man the organism produces the disease known as epidemic cerebrospinal meningitis. In this there is an exudation into the inner meninges of the brain and cord. The exudate may be purulent, sero-purulent, or fibrino-purulent. The most marked lesions are found at the base of the brain, extending from the optic commissure backwards over the crura, the pons, and the medulla. The meninges of the entire brain are rarely affected; the exudate on the convexity is usually most extensive on the lateral surfaces, extending for some distance on either side of the fissure of Rolando. The exudate varies in character according to the acuteness of the process. In the most acute cases there is but little exudation, in the more chronic there is often a considerable amount, and it contains a great deal of fibrin. The exudate always contains numbers of large endothelial cells which are phagocytic for the leucocytes. In chronic cases there is considerable thickening of the meninges, due to the formation of granulation and connective tissue. The process in the meninges of the cord is the same as in the brain. The exudate is chiefly in the meninges on the posterior surface of the cord, and may be confined to this locality. There is proliferation of the cells of the neuroglia both on the surface of the brain, in and

beneath the ependyma of the ventricles, and in the vicinity of the foci of softening and hæmorrhage in the white and gray matter. Nuclear figures also are found in the neuroglia cells at a distance. The ganglion cells of both the brain and cord show degenerative changes.

From the brain the exudation extends outwards along the various cranial nerves. The most marked lesions are found in the second, the fifth, and the eighth nerves. In the optic nerve the exudate is contained in the pia arachnoid, the subdural space of the nerve being affected. The exudation may extend into and destroy the eye. The exudation often extends along the auditory nerve into the internal ear, and from this to the middle ear. It extends along the fifth nerve to the Gasserian ganglion. Both the nerve and the ganglion become infiltrated with the purulent exudate, and the ganglion cells are degenerated. The spinal ganglia also show purulent exudate and degeneration, the process extending to them along the roots of the spinal nerves.

In a small number of cases foci of pneumonia, with purulent exudation due to the same organisms are found. The foci generally are small.

It is not known how the organisms find entry into the meninges. In a few cases acute coryza has been found, and it has been supposed that the cocci may make their way into the meninges from the nose by means of the lymphatics. The number of micrococci found varies greatly in the different cases, but they always are more abundant in the more acute cases. They are almost exclusively found within the polymorphonuclear leucocytes. The few which are found outside the cells in smears from the exudate come from cells which are ruptured in making the preparation. They also may be found in considerable numbers in the exudate from the middle ear when this is involved by the extension of infection from the meninges. The organisms are found in much greater numbers in the focal pneumonia accompanying meningitis than in the exudation in the meninges. The infection of the lungs is secondary to the infection of the meninges, the cocci reaching the lungs either by the blood or by the bronchi after preceding infection of the middle ear and Eustachian tube.

Other infections by this organism, both in connection with meningitis and independently, occur, but they are rare.

## A CASE OF ACUTE EPIDEMIC CEREBROSPINAL MENINGITIS.

Anatomical Diagnosis. Acute epidemic cerebrospinal meningitis.

White, male, age two years. On December 1st, the child was supposed to have fallen from a trunk or to have been knocked down by a suddenly opened door. This happened at 5 P.M. Child ate supper, and slept fairly well. The next morning refused to eat, became unconscious at 9 A.M., and remained so until death. At 11 A.M., had a tonic convulsion which lasted one minute, all extremities being equally affected. In the following eight hours had ten similar convulsions and vomited several times. At 8 P.M., December 2, lumbar puncture was done and 40 c.c. of turbid fluid obtained, the fluid being under increased pressure. Death, a few hours later.

Body well developed and well nourished. Lividity of skin marked in the posterior dependent portions of trunk and extending to the face and front of chest. The anterior surface of chest shows decided mottling of the skin, but no evident eruption. Slight rigor mortis.

All the organs of the body perfectly normal with the exception of the brain. The bladder was distended and reached half way to the umbilicus.

Head. Anterior fontanelle open, sagittal and coronal sutures not yet fused. Sinuses contain fresh blood clots. The inner surface of dura moistened by a slight amount of yellowish fluid exudation. There is a thick purulent exudate in the pia arachnoid, most marked along the course of the vessels. The exudate is most abundant at the base of the brain and over the superior surfaces of the parietal lobes. The cortex in contact with the exudate is slightly injected and softer. The vessels of the pia greatly congested. The lateral ventricles contain a turbid blood-stained fluid. The basal ganglia are unchanged.

Spinal cord. The pia of the entire cord is cloudy and lustreless. In the lumbar region beneath the dura there is a considerable amount of cloudy blood-stained fluid.

Smears and cultures from the exudation showed abundant Gram negative diplococci. In the smears they were chiefly within the polynuclear leucocytes.

REMARKS. A very typical case of acute epidemic cerebrospinal meningitis. The clinical history is given to show how short period of symptoms may be. It is very possible that the fall which was described may mark the first symptom, or it may have no relation to the attack. The exudate is unusually large for so acute a case.

## GONOCOCCUS

This is a coccus occurring always in pairs, the single cocci flattened slightly at the side of contact. It is an exclusive parasite of man. The organism is cultivated with difficulty and only on special media. The temperature limits of growth are 30 and 38° C.

The urethra of the male and female, the conjunctiva in the newborn, the vagina, uterus and tubes are the most susceptible tissues. Infection is almost invariably through coitus. The infection may extend from the urethra in the male to the prostate and epididymes, and in the female to the uterus, the tubes and the glands of Bartholin. Local peritonitis involving the pelvic peritoneum and resulting in extensive adhesions results from extension of infection from the Fallopian tubes. Extension to the bladder and kidneys occurs but is not common. The organism may enter into the blood and be carried to the joints, the synovial membrane being susceptible to the action of the organism. Acute endocarditis may be produced also. These remote infections are more common in the male, probably owing to the better opportunity for blood infection.

The infection of the Fallopian tubes produces serious and extremely chronic conditions. The tubes in the chronic state are enlarged and tortuous, the wall greatly thickened by an increase in tissue and oedema. The exterior surface frequently is covered with adhesions and these may mat together uterus, tubes and ovaries. The lumen is dilated, the papillary folds of mucous membrane are irregular and the epithelium may be in large measure lost. Leucocytes, desquamated epithelial cells and large endothelial cells containing fat are found in the lumen. Beneath the surface are large numbers of plasma and lymphoid cells. In the wall are foci of lymphoid cells which may take the form of definite lymph nodes with germinal centres and sinuses.

In acute infections gonococci are found in large numbers and chiefly in the pus cells. In the chronic infections they are difficult to find. Apparently a very low grade of infection is present in chronic cases, few organisms with a very low degree of virulence living on the surfaces, as the staphylococcus may live on the skin,

but the gonococci from these cases when implanted on a fresh soil can quickly regain virulence.

#### A CASE OF GONORRHEA WITH GENERALIZATION OF THE INFECTION

**Anatomical Diagnoses.** Acute gonorrheal urethritis, prostatitis, synovitis, pericarditis, myocarditis and endocarditis; Perforation of the heart; Hæmorrhage into pericardium.

White, male, age thirty years, admitted to hospital September 30th. A urethral discharge noticed four weeks before admission. Ten days after this the left knee began to swell and became painful. After four days the right knee became similarly affected. Since this he has had pain and swelling in fingers, shoulder and ankles. There is pain in the chest on deep inspiration. On October 6th, pain in chest ceased. On October 7th, he complained of increased pain in chest. There was a slight increase in cardiac dullness, no murmur or pericardial rub. October 8th, continued pain in chest; October 9th, slept well, awoke at 6 o'clock and drank some milk. At 7 o'clock he cried out as if in pain and fell out of bed. The house officer found him gasping for breath and no pulse perceptible at wrist. Died immediately after being seen. The temperature during the whole course of the attack did not exceed 99½. The pulse was under 110.

Autopsy twenty-six hours after death. The body of medium size, slightly built, badly nourished. The general surface cyanotic. Both knee joints, especially the right, enlarged and fluctuation is evident. The subcutaneous fat small in amount, muscles pale.

Peritoneum smooth. No adhesions. Both lungs free from adhesions.

The pericardium enormously distended. The external surface congested and covered with small hæmorrhagic foci. In the pericardial cavity there is 800 c.c. of bloody fluid in which there are large masses of clot. On removal of this both the surfaces of the pericardium are covered with fibrinous exudation containing foci of hæmorrhage.

The heart is firmly contracted. The myocardium of left ventricle is firm and in places of a peculiar waxy color somewhat resembling amyloid. About the bases of the papillary muscles the tissue has a gray translucent gelatinous appearance. This is especially marked at the apex of the ventricle and in places is associated with hemorrhage. This condition of the myocardium is almost confined to the left ventricle. There is some evidence of it on the right side, but it is not so well marked. On the interior surface of the left auricle there is an area 2 by 2.5 cm. where the muscular tissue is pale, opaque and softened. In the centre of this there



is an irregular, small perforation 2 mm. in diameter. The valves are normal, the coronary arteries smooth.

The spleen is enlarged, the follicles prominent.

Liver and kidneys slightly enlarged and cloudy.

Pancreas normal.

Gastro-intestinal canal. Stomach normal. All the follicular tissue in large and small intestine is enlarged and hyperæmic. In the small intestine the single follicles project almost as small polypi. The Peyer's patches are enlarged and smooth on the surface. All the mesenteric lymph nodes are enlarged.

The lungs are hyperæmic with slight œdema in posterior portions. Bronchial lymph nodes slightly enlarged.

The right knee joint is greatly distended. On section about 100 c.c. of viscid, rather transparent pus escapes. The synovial membrane of joint swollen and intensely congested. Papillary fungoid masses of granulation tissue extend into the joint from the synovia, having somewhat the appearance of tuberculous granulations. These masses have a pale and opaque surface and below this the tissue is œdematous. The muscles in the vicinity of the joint are œdematous. The left knee joint is similarly affected.

Genito-urinary system. Bladder somewhat distended, mucous membrane pale and normal. The entire mucous surface of the urethra is thickened and dense. About 4 cm. from the meatus there is a slight loss of substance on the surface. The mucous surface is covered with a slight purulent exudate. The prostate is enlarged. On section there is a general purulent infiltration of the tissue and on the left side a distinct abscess. The seminal vesicles, testicles, and epididymes show no alteration.

Microscopic examination of the pericardial exudation shows in addition to the blood large numbers of pus cells and large endothelial cells. No gonococci are found in the pus of the exudate. The examination of coverslips from the urethra, from the knee joint and from the abscess in the prostate shows gonococci. They are abundant in the urethra, but comparatively few are found in the joint. The organisms are contained only in pus cells and morphologically and in staining are identical with gonococci.

Microscopic examination of sections of the urethra shows here and there slight losses of substance in the mucous membrane. Among the epithelial cells there are numbers of polynuclear leucocytes and many of these on the surface contain gonococci in characteristic arrangement. The tissue immediately beneath the mucous surface along almost the entire length of the urethra shows an intense infiltration with lymphoid

and plasma cells. No gonococci are found in the submucous tissue nor in the deep layers of the epithelium. The cells of the mucous membrane throughout are swollen, more or less desquamated, and in places entirely absent, the granulation tissue appearing on the surface. The gonococci are more abundant where the purulent infiltration of the tissue is most intense. They are found in the crypts of Morgagni, but are less numerous here than on the surface. Sections of the membranous portion of the urethra near the prostate show the same condition. In the ducts of the prostate there is a purulent exudate with but few gonococci. The prostatic tissue shows an intense purulent infiltration with focal destruction of epithelium. On one side the tissue is softened and broken down into an abscess.

Sections from the heart show an intense pericarditis. The pericardium is thickened, swollen and infiltrated with polynuclear leucocytes. In places there are small amounts of fibrin on the surface. In the most degenerated part of the myocardium of the left ventricle, there is extensive purulent infiltration and necrosis of muscle fibres. In places the exudate is distinctly hæmorrhagic in character. In the left auricle there is a large area of necrosis and purulent infiltration which involves the entire thickness of the wall. In this area there are great numbers of gonococci within the pus cells. In the area around the rupture necrosis of the myocardium is complete.

The sections of the granulation tissue in the knee joint show a purulent exudation on the surface extending a short distance into the tissue. Below this the tissue is of the type of very vascular connective tissue. Gonococci are found in small numbers, never deep in the tissue, but always immediately on the surface or in the most superficial layers.

**REMARKS.** The case is primarily one of gonorrheal infection. The urethral lesions show a purulent exudation with acute degeneration and desquamation of the mucous surface and a very marked reaction in the tissue beneath. The condition involves the entire urethral surface including the urethral pouches. The gonococci are confined to the surface and are in the interior of the pus cells; the infection has extended from the urethra into the prostate. More frequently the extension is into the epididymis. It is easy to understand from the situation of the gonococci the persistency of gonorrheal infection, for in the crypts of the mucous membrane they cannot be reached by therapeutic applications. Infection of the joints by way of the blood is not uncommon in gonorrhea. Here much the same conditions are produced as in the urethra.

The gonococci grow on the surface and do not invade. The condition of the heart is interesting. There is here an acute pericarditis with a fibrino-purulent exudate. The pain which the patient complained of in the pericardial region is due to this. The evidence of the exudation is also seen in the increased dullness over the cardiac area. The infection of the myocardium resulting in increased purulent infiltration and hæmorrhage is an unusual manifestation of the gonorrheal infection. The valves of the heart are more frequently the site of the infection. The perforation of the heart through the softened area in the auricle took place probably a few minutes before the death of the patient adding the hæmorrhage to the mass of pericardial fluid, the pressure from which was already interfering with the heart's action. It is also interesting to see the large amount of fluid which was in great part not due to the hæmorrhage but to the exudation.

## BACILLUS TUBERCULOSIS

Although four types of the tubercle bacilli are recognized, the human, the bovine, the fowl and the piscian, only the human and the bovine are pathogenic for man. These two types are differentiated by their cultural peculiarities, their infectiousness and to some extent by their morphology. The human bacilli grow more readily than the bovine, the surface of the growth is dryer and more nodular and they are less pathogenic for laboratory animals, particularly the rabbit, than are the bovine bacilli. Morphologically the human bacilli are somewhat longer and show more variation in size than do the bovine.

The tubercle bacilli are slender rods usually somewhat curved and, in the tissues, tend to occur in small groups of as many as a dozen, the single bacilli often parallel, or in large masses. They are found both within cells and free. The bacillus is a parasite only, adapted for a certain narrow environment. It is the type of the acid fast bacilli, stains penetrate the outer covering with difficulty and are not removed by the action of acids. Of the laboratory animals the guinea pig is the most susceptible. The fluid of cultures free from bacilli has slight pathogenic properties, but the chief action of the organisms is due to endotoxines.

The mode of infection in man is obscure and the bacilli can enter by a number of routes. It usually is assumed, from the frequency and the extent of the lesions in the lungs, that infection, in the majority of cases, takes place by inhalation of bacilli. The bacilli can enter the body, without the production of lesions at the point of entry, and be carried to remote parts, such as the bones or lymph nodes, and there produce lesions. Infection may take place from the mucous membrane of the mouth and the alimentary canal. The organism may also enter the skin by means of the natural openings, or through lesions produced by trauma. Infection by the skin plays but little part in the disease although local lesions may be produced. Infection through the placenta can take place, but is infrequent. Bacilli have been found in lesions of the placenta and in the tissues of the foetus; extensive lesions have also been

ound in the organs of children so young that placental infection must be assumed.

Susceptibility to infection seems to vary in different individuals. Certain families are more prone to the disease. The great frequency of tuberculous lesions, which is found at autopsies (safely reckoned at two thirds of all adults) and the great frequency with which healed lesions are found, show that the differences in individuals is rather a matter of tissue resistance to the extension of the tuberculous process, than of resistance to infection. The general resistance varies at different ages and at different periods in the course of the disease. The chronic forms of tuberculosis tend to remain quiescent for considerable periods and then to extend suddenly. The different tissues of the body vary greatly in their resistance to the action of the bacilli. The muscles, the brain, the ovaries, the testicles and the pancreas are the most resistant tissues. These tissues rarely are primarily attacked but may be affected by the extension of a tuberculous process in the vicinity.

The usual effect produced by the tubercle bacilli is proliferation of the fixed cells of the tissue with the production of large cells of the endothelial type. These cells may be formed from connective tissue cells, from certain epithelia as the epithelium of the lung alveoli, and from the endothelial cells of the blood and lymphatic vessels. It is probable that they most frequently are of endothelial origin. The tubercle bacilli are found both in and between these cells. Associated with these cells are giant cells. These are large protoplasmic masses with a number of nuclei which are arranged either at the extremities of elongated cells or around the periphery of round or irregular cells. Giant cells are so commonly present that they constitute one of the landmarks by which tuberculous tissue is recognized. Giant cells are formed from the fusion of large endothelial cells. Between these cells there is often the appearance of reticulum. This reticulum is in part connective tissue representing the old connective tissue between the original cells and in part is newly formed. The appearance of reticulum is often given by the extension of the branched processes of the giant cells.

**MILIARY TUBERCLE.** Such a tissue, composed of endothelial and giant cells with or without a reticulum, may be present in small masses from 0.1 to 1 mm. in diameter. They never contain blood

vessels and have a pale gray color. The disease tuberculosis takes its name from the presence of these small nodules or tubercles. Around the periphery of the tubercle a tissue is formed containing cells similar to those of granulation tissue, namely, lymphoid, plasma and endothelial cells. Degenerative changes in the tubercle are constant. There is fatty degeneration of the central cells and of the giant cells, which may be recognized in fresh sections by fat stains. The most characteristic form of degeneration is that known as caseation. In this the contour of the individual cells is lost and they become fused together into a soft, granular mass containing nuclear fragments. The caseation often is preceded by fatty degeneration, a fatty ring appearing around the central caseous mass. Even in the giant cells caseation takes place in the centre, often surrounded by a fatty ring. The giant cell in this way in itself represents a type of a tubercle. Leucocytes enter into the formation of the tubercle only when the central caseation takes place, and may be found around the periphery of the caseous mass.

**CONGLOMERATE TUBERCLE.** Miliary tubercles tend to increase in size by peripheral growth to only a very limited degree. This may be due to the fact that the cells at the periphery gradually acquire a resistance to the action of the bacilli. The increase in size of the nodule is by continuous formation of miliary tubercles in the periphery. This is due to the conveyance of tubercle bacilli from the parent nodule into the surrounding tissue where they set up similar centres of growth. In this way nodules of considerable size may be formed, the whole centre becoming caseous by the extension and fusion of the caseous centres of the individual tubercles. Most of the tubercles which are large enough to be seen by the naked eye are conglomerate in character. Very large conglomerate tubercles tend to form in resistant tissues as in the brain.

**DIFFUSE TUBERCULOUS TISSUE.** The same sort of tissue which is found in the miliary tubercle may form diffuse masses. There is not a sharp separation between such a mass and the surrounding tissue. Giant cells in variable numbers may form among the endothelial cells, more generally at the edge of the area. Irregular areas of caseation appear, the single areas often joining and forming a network through the tissue. The best examples of such diffuse formation of tuberculous tissue is found in large tuberculous lymph nodes and in tuberculous synovitis.

**TUBERCULOUS EXUDATE.** With cell proliferation in tuberculosis there is exudation to a greater or less degree. The amount and character of the exudate varies; it may be so abundant that it is the most prominent change and masks the proliferation; it may be composed of polynuclear leucocytes and have all of the properties of the purulent exudation. Very commonly there is considerable fibrin in the exudate and the remains of fibrin may be found in caseous tissue. In the lungs there is often found a peculiar sort of serous exudation. In this the alveoli are filled with a viscid, more or less gelatinous, clear, transparent material. This is not peculiar to tuberculosis, but is found more commonly in association with this than with any other process. Tuberculous exudates are found more commonly in certain parts of the body than others and are especially prominent when surfaces are affected. In tuberculosis of the lungs, the meninges and serous surfaces, there usually is a large amount of exudate. In the lungs just as definite fibrinous exudate may be found in the air spaces as after infection with the pneumococcus. Miliary tubercles may form on surfaces and afterwards be covered by an exudate. Red blood corpuscles may be so abundant in the exudate as to give it a hæmorrhagic character. In tuberculous pneumonia the exudate undergoes the same fate as the tuberculous tissue. It does not undergo autolysis, but becomes caseous. The large caseous areas found in the lung are due rather to caseation of the exudate and the tissue which contains it than to the caseation of definite tuberculous tissue.

**CICATRIZATION.** Around the tubercle there is a tendency to the formation of cicatricial connective tissue which is resistant to the action of the bacilli and tends to prevent the extension of the process. The more resistant the animal and the tissue the greater is the tendency to the formation of cicatricial tissue. This is dense, resistant, contains few blood vessels or spaces by which the bacilli can pass the encircling wall, and also few cells. Such a tissue can be formed inside of the tubercle by the formation of intercellular substances from the cells comprising its structure. This tissue can also become caseous, but the caseous mass is firm and differs from that formed by degeneration of the cells. Tuberculosis does not heal by the destruction of bacilli or their removal, but by connective tissue masses forming a resistant wall around the lesion. It is not uncommon to find in the lungs, or elsewhere in the body, masses

of tuberculous tissue which have undergone caseation and become walled off by a firm mass of cicatricial tissue. It is not known how long tubercle bacilli can live enclosed in such a mass. The most rapidly fatal forms of tuberculosis are those in which the exudative processes form the chief lesions.

The mass formed by the caseation of tuberculous tissue and exudate may remain in an unchanged condition. When composed chiefly of cells it is soft and easily broken down, but is firmer if connective tissue has entered into its formation. Lime salts may be deposited in the caseous material and the nodule become calcified. This is a conservative process and tends further to prevent dissemination. A much more unfavorable process is softening. By this the comparatively firm, caseous mass becomes changed into a soft, semifluid material. It is not absolutely known upon what this softening depends. It may be due to the action of ferments within the caseous material, as in the softening of the thrombus, or it may result from the action of other organisms which secondarily invade. The great danger of tuberculous softening is that the softened material, carrying the bacilli, may find its way into the adjoining normal tissue extending the infection.

**THE RELATIONS OF TUBERCLE BACILLI TO THE PROCESS.** The number of tubercle bacilli which are found in the lesions varies enormously. They are present in the greatest numbers where the process is most active and most exudative in character. Large numbers may be found within the endothelial cells or within the giant cells. When tubercles develop in resistant tissue, very few bacilli will be found. In certain cases they may be found in the tissues without any reaction about them. Very few are found in old lesions enclosed in cicatricial tissue. That they are contained in such tissue is shown by its infectiousness when injected into a susceptible animal.



## FORMS OF TUBERCULOSIS

**GENERAL MILIARY TUBERCULOSIS.** In nearly all cases of tuberculosis a few bacilli enter into the blood and are carried by this into distant organs. In miliary tuberculosis the tubercle bacilli usually are carried into the tissue by the blood route. Large numbers of bacilli entering into the circulation are carried into all of the tissues and give rise to the formation of great numbers of small tubercles. These are most abundant in the lungs, liver, spleen and on serous surfaces. They are less abundant in the kidneys and usually are absent in the brain, the wall of the alimentary canal, the muscles and the skin. Such a general infection takes place from some focus in the body where the tuberculous tissue is in the interior of the vessels. This may be due either to the extension of tuberculosis outside of the vessel or to infection of the endothelium. In the latter case large mural thrombi may be formed within the vessel; the bacilli find in the masses of thrombus suitable conditions for growth, and from this source either an instantaneous extension of the bacilli into the circulation takes place, or they may pass into the circulation at intervals. In rare cases such an enormous number of tubercle bacilli may be found in the circulation that it seems evident that they multiply in the blood or in the endothelial cells at numerous places. Cases also are found in which there is extensive tuberculosis of the thoracic duct from which place the bacilli can enter the circulation. In certain cases a tuberculous aneurysm forms. In this the tuberculous focus is formed on the exterior of the vessel the infection coming from one of the vasa vasorum or from a tuberculous lymph node. By the extension of the process to the wall of the vessel, this becomes weakened and a tuberculous aneurysm is formed. Both in the wall of the aneurysm and in the thrombus which it contains there may be immense numbers of bacilli which easily enter the blood. The formation of acute miliary tuberculosis does not, however, depend solely upon the opportunity of infection by means of the blood. Rarely cases are seen in which large numbers of tubercle bacilli may be demonstrated in the circulation without the formation of

miliary tubercles. In these cases it must be assumed that either the tubercle bacilli are devoid of virulence or that the tissues are resistant to their action. In the most marked cases of acute miliary tuberculosis the disease runs its course in a very short time, with fever and the general clinical characteristics of an acute infectious disease, and the organs are filled with very small gray miliary tubercles in most of which caseation has not yet taken place. In contradistinction to the cases in which the resistance of the tissue is apparently high, rapid cases are encountered in which the tubercles take the form of small foci of exudation often combined with single giant cells and contain numbers of bacilli.

**CHRONIC MILIARY TUBERCULOSIS.** In certain cases the disease runs a more chronic course, the tubercles are not so numerous, are larger and more advanced in caseation. This form of disease is more common in children than in adults and is probably due to few bacilli entering into the circulation.

**PARTIAL DISSEMINATED MILIARY TUBERCULOSIS.** In this the miliary tubercles are limited to certain organs or even parts of organs. It is often seen in the lungs and is due to a few tubercle bacilli entering the circulation and being retained in the first capillaries they encounter. Occasionally, in an organ there is a circumscribed formation of miliary tubercles in an area having the form of an infarction. This is due to tuberculosis of the artery supplying this territory or the lodgment in it of an embolus which contains bacilli but which does not completely occlude the vessel. The bacilli are then distributed in the area supplied by the artery.

**LOCAL TUBERCULOSIS.** In this form the tuberculosis tends to remain limited to the focus in which it started. Foci of tubercles, which have become completely walled-off, preventing further extension, may be found in any organ, but are more common in certain organs than in others. In other cases there is a tendency to local extension, but little or no tendency to generalization. The best examples of this are seen in tuberculosis of the skin and bones. It is due to the tissue not offering suitable conditions for the rapid growth of the bacilli or to the fact that the anatomical structure of the part does not offer favorable conditions for dissemination.

**TUBERCULOSIS OF THE LUNGS.** In no organ of the body are such constant and extensive lesions caused by tuberculosis, and

in none are there such opportunities for dissemination. This is due to the extent of the surface and the opportunities by means of the bronchi, lymphatics and blood vessels for the distribution of bacilli within the organ. The bronchi form the main channel for the extension of infection, but not the only one. Infection may extend along the lymphatics. The blood vessels are extremely abundant. Tuberculosis of the larger vessels is not uncommon and this must be true also of the smaller vessels and capillaries. The abundance of the exudation in the process gives material in which the tubercle bacilli can multiply. The lesions caused by tuberculosis are further intensified by the action of other organisms, particularly the pathogenic cocci, which find in the lesions produced by the tubercle bacilli favorable conditions for their own action. In chronic tuberculosis of the lung there is an infinite number of changes which give a great variety to the lesions. Certain processes can be singled out and described separately, but they may all take place together.

In marked cases of *general miliary tuberculosis of the lungs* the lungs do not collapse on opening the chest. They are heavier than normal and parts almost sink when thrown into water, but air is never wholly absent. They usually are greatly congested and of a dark red color. The congestion is more pronounced in the lungs of adults than in children. The pleural surface usually shows grey, often transparent, tubercles. They may be evenly distributed over the surface or may be more abundant in places. On section of the lungs the tubercles stand out from the cut surface and they may be felt as small projecting points. They are rather more abundant, particularly in children, in the lower than in the upper lobes of the lung. On microscopical examination the tubercles vary in size and in the extent of the central caseation. The periphery usually is not round because the joining air spaces take part in their formation and become partly occluded by cells. Even in the formation of miliary tubercles there may be a considerable amount of exudation in which fibrin is present. Giant cells usually are present and may be formed from the cells lining the air spaces, in which free-lying giant cells are occasionally found. The tubercles often are in considerable numbers in the connective tissue, in the walls of the bronchi and blood vessels. Not infrequently they are found in the interior of small vessels, projecting

from the intima. The tubercle bacilli reach the tissue by means of the blood vessels, and the process begins in the vascular endothelium. The occlusion of the blood vessels, which is so striking on the injection of the blood vessels of the lung, is due to the proliferation of endothelium. Miliary tubercles are constantly present as a part of all tuberculous processes in the lung. They are often distributed around the larger areas due to the dissemination of the tubercle bacilli by the lymphatics. It is not uncommon to find large areas of extensive tuberculous broncho-pneumonia and around these miliary tubercles in such numbers that the separate foci blend together. Conglomerate tubercles are common also, and in the more chronic form of miliary tuberculosis the majority of the tubercles are conglomerate; in each several centres of caseation may be recognized. All of the tuberculous processes may be accompanied by the formation of diffuse tuberculous tissue composed of epithelioid and giant cells, more or less exudation and irregular areas of caseation.

CASEOUS TUBERCULOUS PNEUMONIA is essentially a process of exudation. The exudation varies in character. It always contains a considerable amount of fibrin in which there are numerous cellular elements. These cells are in part due to exudation and in part to proliferation of the lining epithelium. The entire area of the lung affected, both exudation and the tissue containing it, undergoes caseation, by which it is converted into a comparatively soft, whitish gray mass which may have a more or less slaty color from the presence of pigment. These areas vary in size and distribution. They may be so small as to simulate miliary tubercles, or the process may involve an entire lobe or even an entire lung. The larger areas may be due to confluence of small areas or to the simultaneous infection of all parts of the lobe. The areas usually are irregularly distributed, one or both lungs being affected. They are more common in the lower lobes than in the upper. In the caseous tissues the walls of the air spaces usually can be recognized. In rare cases exudation may be composed entirely of polynuclear leucocytes, the whole focus resembling an abscess, and in these cases there are immense numbers of tubercle bacilli within the leucocytes.

TUBERCULOUS BRONCHITIS AND PERIBRONCHITIS occurs in caseous pneumonia because all the bronchi included in the areas are

affected in the same way as the air spaces. In certain cases the bronchi are affected chiefly and there is a direct extension through the wall into the surrounding lung tissue. The bronchi may be filled with exudate and proliferated cells. The epithelium may be entirely lost, or adhering masses of the cylindrical cells may be mingled with the contents. Definite tuberculous tissue forms in the bronchial wall and projects into the lumen. In certain cases the bronchus seems to be affected secondarily to the surrounding tissue. The infection of the bronchus may result not from the interior but from extension of tuberculosis of the peribronchial tissue due to lymphatic infection. There may be a considerable formation of miliary tubercles immediately around the bronchi in these cases. The bronchi may be recognized in longitudinal section as caseous branching streaks or in transverse section as solid caseous masses with miliary tubercles about them.

There is a greater tendency in the lung than elsewhere for the caseous material to undergo softening. The softening is sometimes associated with the presence of great numbers of tubercle bacilli and an invasion of the caseous tissue by leucocytes. Cavities are formed in consequence of softening. The presence of these cavities and the evident destruction of the tissue has given the name *phthisis* to chronic ulcerative tuberculosis of the lung. The cavities vary in form and size. The softening may take place rapidly in the pneumonic areas and a series of irregular branching cavities, corresponding to the areas of pneumonia, may be formed. All of the tuberculous cavities of the lung open into bronchi. The cavities when once formed can increase in size by the extension of the tuberculous process about them and the continuation of the softening. In a large area of tuberculous pneumonia there may be a simultaneous formation of several cavities which coalesce by extension. In other cases the cavity ceases to enlarge, the softened material is discharged and dense cicatricial tissue may form in the wall. There may be slow formation of miliary tubercles or of tuberculous tissue in the wall, with very slow extension of the caseation, and in still other cases the cavity may be lined with a vascular granulation tissue without tubercles. In the extension of the softening and cavity formation there is a difference in the resistance of different tissues. The connective tissue cells of the vessels are more resistant than the intervening lung tissue and these

are frequently left as bands traversing the cavities or projecting from the walls. Coincident with the cavity formation the tuberculosis extends. The softened material contains numerous tubercle bacilli which enter into the bronchi and may be carried into different parts of the same or both lungs. The walls of the cavities sometimes serve as breeding places for the bacilli, these growing on the surface as in pure culture.

New formation of connective tissue, which must be regarded as reparative in character, constantly accompanies the process. It may form such a marked feature that the name *fibroid phthisis* may be applied. The new formation of connective tissue produces great thickening around the vessels and bronchi and bands of connective tissue are given off which traverse the lung and in part compress and in part fill up the air spaces. In such connective tissue the remains of air spaces are seen as more or less irregular spaces or slits lined with a low cylindrical columnar epithelium, the structure resembling glands. Most of the capillaries in the walls are occluded and such areas probably take but little part in respiration. Changes in the blood vessels constantly accompany the process. The large vessels in the areas affected become occluded by the formation of connective tissue within them. In no place can the compensatory endarteritis which takes place on the diminution of a vascular territory be so well seen as in such lungs. A large blood vessel may have its lumen many times reduced by this process. Rupture of large blood vessels of the lung from weakening of their walls by the destructive process is comparatively rare. The small hæmorrhages which are so common in lung tuberculosis are due usually to rupture of small vessels or to a hæmorrhagic exudation. Thrombi usually are formed before the large vessels are opened by ulceration or they become occluded by obliterating endarteritis. When a large vessel joins a tuberculous cavity a thrombus may form, or the wall where weakened by the extension of the tuberculous process may gradually give way, resulting in the formation of an aneurysm which projects into the cavity. Severe and fatal hæmorrhages sometimes result from the rupture of such aneurysms.

There are other conditions in the lung not due to the tuberculous process in itself, but to the conditions produced by the tuberculosis. Atelectasis may be caused by the occlusion of bronchi by caseous

masses either formed there as an exudate, or brought from some other parts of the lung. The area of lung supplied by the bronchus collapses because of the absorption of the air. Emphysema also is extremely common, due to expansion of the areas of lung which adjoin the tuberculous foci.

**TUBERCULOSIS OF MUCOUS MEMBRANES.** The type of tuberculosis here is the tuberculous ulcer. This has much the same characteristics wherever formed. It varies in size and depth, the edges are irregular, often elevated and undermined. The base is irregular and usually small elevated gray or yellowish-white masses (miliary tubercles) are seen on and beneath the surface. The ulcers are due to the formation of tubercles or tuberculous tissue beneath the epithelium and to the necrosis of the overlying surface. The ulcer extends laterally and in depth by continued formation of tubercles and softening of the caseous centres. There is a continuous slow and irregular destruction of tissue. In the trachea the ulcers usually are small and shallow. They may be confluent resulting in large shallow ulcers with a rough base which may cover the entire posterior wall of the trachea. In the larynx the ulcers are smaller, deeper and more undermined. Such ulcers are secondary to tuberculosis of the lungs and are produced by the infection of the surface by the tubercle bacilli in the sputum. In tuberculosis of the tonsils the infection takes place from the crypts. The tonsils undoubtedly form a point of entry for the tubercle bacilli in certain cases. The tubercles are formed in the lymphoid tissue surrounding the crypts. Tuberculous ulcers are common in the alimentary canal and are found there in their most characteristic form. In the small intestine they have much the same distribution as the typhoid ulcers. Unlike these they generally have their greatest diameter transverse to the long axis of the intestine due to the process extending in the course of the lymphatics. They can be distinguished from other forms of ulceration by the presence of miliary tubercles in the peritoneum immediately over them. Tuberculosis of the alimentary canal is almost always secondary to tuberculosis of the lungs, the sputum carrying the infection; but it may be primary, especially in children. Tuberculous ulcers in the oesophagus, stomach and upper fourth of the small intestine are extremely rare.

**TUBERCULOSIS OF THE GENITAL SYSTEM** is rather more common

in males than in females. In the male owing to the intimate connection between the genital and urinary organs there rarely is infection of one system without infection of the other. In the female there is not the same opportunity for infection to extend from one set of organs to the other. In genital tuberculosis in the male the infection may be primary, or secondary to a tuberculous process elsewhere in the body. The primary infection takes place usually in the epididymis. There seems little probability that bacilli can enter the epididymis from the urethra. The infection is due to a deposit in the epididymis of bacilli from some point of concealed infection in the same way as infection of the bones undoubtedly takes place. The head of the epididymis is the seat of the most extensive lesions. The tail may be slightly affected or escape. The tubercles and tuberculous tissue are formed in the tissue between the tubules and large conglomerate tubercles often are found. The resulting caseation may be either soft or comparatively firm, depending on the rapidity of the process and the character of the tissue formed. The process may extend from the epididymis into the testicle, but does not occur primarily in the testicle. From the epididymis the infection extends upward along the vas deferens of the cord. This becomes swollen, the epithelium is destroyed and the lumen filled with caseous material. In some cases tubercles are found in the wall, but generally the process is one of exudation and formation of diffuse tuberculous tissue with subsequent caseation. The condition is rarely bilateral. The seminal vesicles become infected by extension from the vas deferens. They become greatly swollen by the formation of tuberculous tissue in the walls and by the filling of the cavities with soft caseous material. One or both vesicles may be affected, the infection extending from one to the other, but they are rarely affected to the same degree. In these cases the prostate shows usually a few caseous foci, but extensive tuberculous lesions comparable to those in the epididymis and seminal vesicles are rare. The urethra is rarely affected. Tuberculosis of the Fallopian tube is more common than tuberculosis in any part of the male genitalia. It may be found in combination with tuberculosis of the uterus or as a primary infection and is commonly bilateral. The tube is often greatly swollen and elongated, the lumen is enlarged and filled with caseous material and the mucous membrane is entirely



destroyed. In minor degrees only a few miliary tubercles may be found in the mucous membrane. In the advanced cases tubercles also are seen on the peritoneal surface. Tuberculosis of the ovary is extremely rare. In cases of tuberculosis of the tubes and in peritoneal tuberculosis tubercles may be found on the surface, but the tissue of the ovary, like the testicle, has a remarkable resistance. Tuberculosis of the uterus usually is accompanied by tuberculosis of the tubes though the reverse is not true. It is more common in the fundus than in the cervix, but the entire uterine canal may be affected. The entire mucous membrane is lost and the surface is covered with opaque and caseous masses, caseation extending a variable distance into the wall and preceded by an enormous formation of lymphoid tissue. Miliary tubercles are rare.

**TUBERCULOSIS OF THE URINARY SYSTEM.** Miliary tuberculosis of the kidney forms a part of general miliary tuberculosis of hematogenous origin. The tubercles are always less numerous in the kidney than in the lung, liver and spleen. They may appear on the surface as small reddish areas of injection, with the small gray points of the tubercle in the centre. They are more numerous in the cortex than in the pyramids and the glomeruli frequently form the point of origin of the tubercles. They have the general structure of miliary tubercles elsewhere. Not infrequently rows of tubercles or longitudinal areas of caseation resulting from their coalescence are found and undoubtedly are to be attributed to the extension of the process by means of the tubules. *Tuberculous pyelonephritis*, is tuberculosis of the kidney combined with tuberculosis of the pelvis and calices and is characterized chiefly by destruction of tissue. *Nephrophthisis* the name sometimes given to this condition indicates the tissue destruction. It appears in various degrees and is more commonly unilateral than bilateral. In the slightest degree it may be confined to a single calyx and its pyramid or may involve the entire pelvis, extending from this to all parts of the kidney. It usually takes the form of diffuse tuberculous tissue with subsequent caseation and softening. The pyramids may be entirely destroyed, each calyx being represented by a tuberculous cavity extending deeply into the tissue or the pelvis may appear as a single cavity lined with caseous material and the kidney tissue be reduced to a thin shell. There has always been a great deal of dispute as to the mode of infection in these cases.

The main process being in the pelvis of the kidney and the pyramids, and the frequent association of tuberculosis of the epididymis, has given rise to the view that the process usually is an ascending one. There is no difficulty in this conception of the infection. The bacilli may extend from the bladder to the ureter, and thence to the pelvis of the kidney by diffusion of bacilli in the urine. With an overdistended bladder there is accumulation of urine in the ureter and pelvis with the production of fluid continuity and in such fluid the bacilli could be distributed by the constant currents which are present. It is possible also that the bacilli may extend from lower down towards the kidney by means of the lymphatics or by the blood. The lymphatic extension has been demonstrated experimentally. In certain cases this ascending infection must be assumed, but it is equally sure that the infection of the kidney can take place by the blood. A few tubercle bacilli may enter the kidney, establish a focus of infection and from this the infection of the calices and pyramids takes place. Tuberculosis of the ureter usually is present in this condition and takes the ulcerative form. There may be numerous small ulcers scattered over the surface or large ulcerated areas due to their coalescence. There is great thickening of the wall due to the formation of tuberculous tissue with extensive surface caseation. Tuberculosis of the bladder may be associated with tuberculosis of the kidney and ureter. The lesions are more pronounced around the ureter of the affected kidney. The area of the trigonum is most affected and the lesions take the character of shallow ulcers with irregular edges. Tubercles in the mucous membrane, without ulceration, may be found in the vicinity of the ulcers.

IN TUBERCULOSIS OF THE LYMPH NODES the bacilli enter by means of the lymphatics. In cases of acute miliary tuberculosis a few tubercles are found in the nodes. They are so prone to infection by the lymphatics that in advanced tuberculosis in any part of the body the corresponding lymph nodes are almost invariably affected. The only exceptions are in that form of tuberculosis of the skin known as lupus and in some cases of tuberculosis of bone. It frequently is primary, especially in the cervical nodes, the bacilli probably entering from the mucous membrane of the mouth or tonsils and producing no lesions at the point of entry. Tuberculosis of the mesenteric nodes also appears without evidence

of disease in the intestinal canal. Lesions in the nodes point to infection by the lymphatics, the first appearance of the tuberculous tissue being in the peripheral lymph sinuses. In certain cases a network of caseous tissue, corresponding in situation to the sinuses, may be formed through the node. Both the miliary form of tuberculosis and the diffuse form are found, the latter being more common. In the miliary form the nodes are enlarged, the capsule thickened, and around the periphery and to some extent in the interior small gray points with caseous centres are seen. Even in these cases microscopical examination will show numbers of large, pale cells in the sinuses with more or less ill-defined caseation. In the other form the lymph nodes are enlarged, the capsule thickened and filled with a soft or comparatively firm caseous mass in which no cells can be recognized. This condition is due to a widespread diffuse caseation of the cells in the lymph sinuses and the intervening lymphoid tissue. In some cases the node may be intersected by bands of newly formed connective tissue. In the capsules there are miliary tubercles or tuberculous tissue with foci of caseation. The extension of the infection may, for a time, be blocked by the lymph nodes, but the bacilli may pass from node to node until the nodes of a part form large adherent pockets. Nodes so small that they ordinarily are not visible may be converted into large caseous masses several centimetres in diameter. The tubercle bacilli may be conveyed along the lymphatics producing no change in these, or the vessel may be filled with a mass composed of endothelial cells, giant cells and exudation. By the resulting caseation they are converted into large white cords with nodular swellings. Such vessels often are seen on the peritoneal surface of the intestine over tuberculous ulcers and extending towards the mesenteric lymph nodes. A process very similar may take place in the thoracic duct. The duct may become greatly enlarged and the lumen occluded, or the tuberculous mass in the wall may project as a thrombus into the lumen.

**TUBERCULOSIS OF SEROUS SURFACES.** The infection may extend from a point of infection on the surface, as an intestinal ulcer, and be hæmatogenous in origin. In cases of acute miliary tuberculosis the process is often very extensive on the serous surfaces which are covered with miliary tubercles often so small as scarcely to be visible. In the peritoneal cavity the tubercles usually are

more numerous in the pelvic peritoneum, the bacilli being carried to this place by gravity. Another favorite spot for their formation is on the under surface of the diaphragm, the direction of the lymph stream here favoring their presence. The formation of the tubercles may be accompanied by an extensive serous exudation which may be the first clinical manifestation of the disease. In the other form of tuberculosis of the serous cavities there is a combination of tubercle formation with extensive fibrinous exudation and organization. The tubercles are formed both on the surface and in the newly formed connective tissue. The process takes place on both visceral and parietal layers which become adherent, forming a mass even a centimeter or more in thickness, which shows on section tubercles, tuberculous tissue, newly formed connective tissue and fibrin or hyalin remains of this. In the pericardium such tuberculous masses may form a serious impediment to the contraction of the heart. Lime salts may be deposited in the caseous tissue. Primary tuberculosis of the serous membranes is probably more frequent in the peritoneum than elsewhere and is more frequent in females than in males which points to the possibility of infection taking place by means of the Fallopian tubes with or without infection of these.

**TUBERCULOSIS OF THE MENINGES.** This occurs as a part of general miliary tuberculosis, or it may be secondary to a focal tuberculous process. It is probably never primary. How the infection takes place is uncertain. Tubercle bacilli may be conveyed by the blood or they may enter by means of the perineural lymphatics, as along the intercostal nerves in tuberculosis of the pleura. The infection usually is more marked in the cerebral than in the spinal meninges though both are affected. Exudation plays a very prominent part in the process. In addition there are tubercles and tuberculous tissue which particularly affect the adventitia and to a certain extent the entire wall of the blood vessels. The parts most affected are the base of the brain, the Sylvian fissure and the superior surface of the cerebellum. The dura is rarely affected. Tuberculosis of the meninges often is accompanied by increased secretion in and dilatation of the lateral ventricles. Dilatation of the ventricles may be produced also by the closure of the valve of Vieussens. Occasionally tubercles may be found extending a short distance along the vessels, but there is

never a miliary tuberculosis of the cerebrospinal tissue. The only form in which tuberculosis is seen here is that of circumscribed larger or smaller masses of tuberculous tissue known as solitary tubercles. They are slow in formation and are conglomerate in character, resulting from the continual peripheral formation of miliary tubercles around a centre formed by the union of the caseous foci. They are more common in the cerebellum than in any part of the brain and are rare in the cord. The solitary tubercles, particularly in the cerebellum, often proceed from a circumscribed infection of the meninges. Great numbers of tubercle bacilli may be found especially when the process is chiefly inflammatory in character. In the solitary follicles they usually are extremely rare.

**TUBERCULOSIS OF THE LIVER** is more common than tuberculosis in any other organ of the body, because wherever the seat of infection a few tubercles usually will be found in the liver. Infection takes place by means of the blood and the extensive capillary circulation favors retention in the liver of any tubercle bacilli which may enter the circulation. The form is almost entirely miliary although large solitary tubercles have been described. The miliary tubercles are situated in the periphery of the lobules, they never attain a large size and a very few bacilli are found in them. The tubercles always are larger in miliary tuberculosis of children than they are in the adult. Another form of liver tuberculosis is that of the bile ducts. In this the infection extends along the lymphatics of the bile ducts leading to formation of diffuse tuberculous tissue in the wall, destruction of epithelium and caseation, the caseous mass being stained with bile. Sections show a softened, bile-stained caseous mass in the centre, and surrounding this a wall of tuberculous tissue with advancing caseation.

**TUBERCULOSIS OF THE BONES AND JOINTS.** This may be secondary to tuberculous diseases elsewhere in the body, but in certain cases is primary. In the long bones tuberculosis begins almost invariably in the marrow of the epiphysis. The process does not really differ from tuberculosis in other tissues. By coalescence and caseation the marrow may be destroyed over considerable areas. Definite tuberculous cavities in the bone can be formed, the trabeculae of the bone being entirely or partly dissolved in the process of softening. The process has many analogies with suppurative osteomyelitis, but is never so extensive. The most common situa-

tion for tuberculosis of the bones is in the bodies of the vertebræ. The disease begins usually near the articulating surface at the anterior portion of the body. The intervertebral substance is destroyed and the infection extends to the adjacent vertebræ. In consequence of such destruction of the bodies of the vertebræ the vertebral column gives way to the pressure forming a knuckle at the point of disease. The infection may extend to the soft parts producing a tuberculous abscess. Infection of the joints always is secondary to tuberculosis of the bones. The entire synovial surface of the joint may become infected resulting in the formation of tuberculous tissue and exudation.

TUBERCULOSIS OF THE SKIN occurs in a variety of forms affecting the different tissues. The most common form is the *anatomical tubercle*. This is an infection of the skin from the surface, which occurs on the hands of those who come in contact with tuberculous material. It consists of a circumscribed hypertrophy of the epidermis and of the papillary layer with great thickening of the papillæ so as to produce a wart-like swelling. Sections show a tissue composed of endothelial cells with slight tendency to caseation and very few tubercle bacilli. The process is extremely chronic and there is little tendency for the infection to extend. The second form is *lupus*. In this there is a formation of miliary tubercles and of tuberculous tissue in the corium. It is associated with a marked new formation of connective tissue and has a slight tendency to surface ulceration. It is exceedingly chronic, it tends to persist and to extend very slowly. A very few tubercle bacilli are found in association with the lesions. The third form is the *tuberculous ulcer* of the skin which does not differ from tuberculous ulcers in the mucous membranes. The process is seated in the subcutaneous tissue; there is undermining of the edges of the ulcers and the formation of tuberculous tissue at the base. In cases of acute miliary tuberculosis in children there often is a peculiar eruption of the skin associated with the process. This appears as small areas of hyperemia surrounding slight papillary elevations. In other cases in the centre of the areas of hyperemia there may be a formation of small vesicles or small crusts due to drying of the surface. On microscopical examination in these areas there is no characteristic tissue reaction. Usually a slight infiltration with lymphoid and endothelial cells with an occasional

giant cell is found. There is little or no tendency to caseation. In other cases there appears to be nothing more than a slight serous exudation. Tubercle bacilli are found in varying numbers and may be in the tissue in considerable numbers without tissue reaction about them. Tuberculosis of the skin has an especial place in the history of the disease owing to the fact that lesions here have but slight tendency to extend. The skin must be regarded as a tissue of very great resistance. Owing to the extent of the surface, tubercle bacilli must in most cases be brought to the skin and yet tuberculous lesions are rare.

#### A CASE OF CHRONIC PULMONARY TUBERCULOSIS WITH TUBERCULOUS MENINGITIS

**Anatomical Diagnoses.** Tuberculosis of lung with cavity formation, discrete and conglomerate tubercles, and tuberculous pneumonia; Tuberculous pleurisy; Tuberculosis of vermiform appendix; Tuberculous meningitis.

White, male, age eighteen years. Body well developed, fairly well nourished. No rigor mortis, body still warm. Slight post-mortem lividity of dependent portions. No oedema. Pupils are unequal. Subcutaneous fat yellow, 1.5 cm. in thickness. Muscles red.

Peritoneum smooth. Intestines somewhat distended with gas. The appendix 9 cm. in length, is uniformly thickened, its distal end clubbed and reddened. It is adherent throughout to the peritoneum lining the ileo cæcal fossa.

The left lung is adherent at apex by firm fibrous adhesions. The right pleural cavity is completely obliterated. Pericardium and heart normal. Coronary arteries and aorta normal.

Throughout the upper lobe of the left lung there are small discrete, conglomerate, tubercles, yellow in color, and slightly raised above the surrounding lung tissue. These tubercles are more prominent and more numerous in the lower margin of this lobe. In the lower lobe there are similar tubercles, but less numerous, and the lung tissue between the foci is somewhat congested. On the pleural surface of the right lung there are numerous tubercles. The lung is firm and noncrepitant except for a small area of tissue in the posterior and lateral aspect of the lower lobe. Throughout all lobes there are numbers of conglomerate tubercles up to 1 cm. in diameter. In other areas in the lung there are solid, firm, completely caseated areas of tuberculous pneumonia. Throughout the upper and middle lobes are numerous cavities with rough, caseous walls

connecting with the bronchi. The largest of these cavities is in the central portion of the middle lobe.

Spleen firm, weight 225 grams. Follicles prominent.

Liver, weight, 1750 grams. Dark red and firm, lobules evident.

Kidneys, combined weight, 360 grams. Surface smooth, dark red.

The gastro-intestinal tract with the exception of appendix is normal. The lumen of appendix is somewhat dilated, and at the distal end there is a small ulcer which extends into a softened tuberculous mass which infiltrates the wall. The peritoneum over this is injected, but otherwise normal. Adrenals normal.

**Brain.** Along the vessels of the pia on the lateral aspect of the brain a few small grayish nodules can be seen. Along the vessels of the Sylvian fissure on both sides these nodules are very much more numerous, the vessels in places apparently converted into caseous cords. The whole tissue of the pia-arachnoid here is thickened and firmly adherent. At the base of the brain between the crura, over the lower surface of the cerebellum and extending to the upper surface, are numerous tubercles along the vessels and a considerable amount of caseous exudation. Both lateral ventricles are dilated and contain an increased amount of slightly turbid fluid. Over the surface of the fourth ventricle there are numerous prominent ependymal granules.

Microscopic examination of the tissue in this case shows in the sections of the brain an extensive tuberculosis of meninges and vessels which at various points extend into the cerebral cortex. Where the exudation is best marked there is increase in the cortical neuroglia.

**REMARKS.** The tuberculous meningitis in this case is extensive and is accompanied by an unusual degree of cortical gliosis. The tuberculosis of the lungs is evidently the oldest focus. An unusual feature of the case is the tuberculosis of the vermiform appendix. Infection here resulted from the tubercle bacilli in the alimentary canal which were contained in the sputum. The infrequency of tuberculosis of the vermiform appendix is rather remarkable in view of the possibility for infection which this would seem to offer.

A CASE OF ACUTE GENERAL MILIARY TUBERCULOSIS  
FOLLOWING TUBERCULOSIS OF THORACIC DUCT.  
EMPHYSEMA OF CHEST

**Anatomical Diagnoses.** Tuberculous ulcers of intestine; Tuberculosis of mesentery glands; Tuberculosis of thoracic duct; General miliary tuberculosis; Subcutaneous emphysema; Streptococcus septicæmia; Pneumothorax.



White, male, age twenty-three years. The body large, fairly well nourished. There is subcutaneous emphysema over the entire thorax and neck. The subcutaneous fat of medium amount, muscles pale.

In the peritoneal cavity a slight increase in the amount of fluid. In the mid-clavicular line the liver is depressed 4 cm. below the costal margin. Diaphragm on right side at sixth rib, on left at fourth.

On opening the chest there is an escape of gas from the right pleural cavity. The tissue of the mediastinum is infiltrated with gas. The pericardial tissue also contains gas, but there is none in the pericardial cavity. There is considerable gas beneath the pleura around the hilum of the right lung. A small amount in similar position in left lung. There is no air beneath the parietal pleura.

Both lungs are free from adhesions. In the bronchi there is a large amount of muco-purulent secretion. Throughout both lungs the tissue is studded with very fine miliary tubercles, homogeneously distributed. Considerable air is contained in the interstitial tissue of the left lung and a small amount is beneath the pleura of the right lung. The tubercles appear as circumscribed, pearly gray nodules up to 1 mm. in diameter. There are no conglomerate tubercles, no caseous pneumonia, no evidence of an older tuberculous process. The bronchial lymph nodes are enlarged and contain in their interior and in their capsules small, scarcely visible miliary tubercles.

The heart is of medium size, the valves and myocardium normal. No gas in the vessels of the body.

The liver is pale, slightly enlarged. Scattered tubercles are visible on the surface and on section.

The spleen is enlarged, the capsule tense, the tissue comparatively soft. Innumerable miliary tubercles, the largest 1 mm. in diameter, are scattered throughout the tissue.

The kidneys are enlarged. On the surface are numerous small pale tubercles with vascular injection of the surrounding tissue. On section scattered tubercles are found.

Gastro-intestinal canal. Stomach normal. About 1 mm. above the ileo-coecal valve there is an ulcer with irregular nonelevated edges. In the base and at the edge of the ulcer there are numerous small points of caseation. Adjoining this larger ulcer there is a small ulcer of the same character. In the vicinity of the valve there are several small and comparatively fresh ulcers. Through the peritoneal surface over these ulcers there are numerous fine sub-peritoneal miliary tubercles. A few tubercles are found on the surface of the pelvic peritoneum in Douglas's cul-de-sac.

The lymph nodes in the mesentery are enlarged, particularly those in the immediate vicinity of the cæcum. On section distinct caseous foci are found within them. The *thoracic duct* in its entire course through the thorax is dilated and filled with a thin, slightly turbid fluid. The upper portion is enlarged to three times its normal size and is solid. The opening into the subclavian vein could not be traced. On opening the duct small tubercles were found at various places on the internal surface. The upper portion of the duct for a distance of 6 cm. is lined with caseous material. In most part the surface of this is smooth and the duct has a complete though irregular lumen. In the upper part the material filling the duct is softened.

Brain and meninges injected, but no tubercles are found along the course of the vessels.

Coverslip preparations from the fluid in the thoracic duct stained for tubercle bacilli were positive. Microscopical sections of the duct showed tubercles in the wall and within the duct caseous material containing numbers of tubercle bacilli in clumps.

Sections of the organs gave the usual picture of miliary tuberculosis. Pure and abundant cultures of streptococci were obtained from heart's blood, spleen, liver, kidney and emphysematous tissue in mediastinum.

**REMARKS.** In this case the subcutaneous emphysema is evidently due to the rupture of the left lung near the hylum allowing the air to enter into the tissue. From here it made its way into the mediastinum and the subcutaneous tissue. It is not improbable that the streptococcus infection originated in this way. The main interest in the case centres in the tuberculosis of the thoracic duct and the relation of this to the general miliary tuberculosis. The infection must be assumed to have been primary in the intestines. The intestinal ulcers represent the only chronic tuberculous process in the body, and the tuberculosis of the mesenteric lymph nodes followed the intestinal lesion. The evident age of the ulcers and the infrequency of intestinal ulceration of hæmatogenous origin is evidence that they are not due to the same source of infection as the miliary tubercles. Histologically, the lesions in the upper portion of the thoracic duct consist chiefly in exudation with caseation, and followed an extensive tuberculosis of the wall. In the masses thus formed tubercle bacilli have grown and from here have entered the circulation.

A CASE OF CHRONIC GENITO-URINARY TUBERCULOSIS  
WITH MILIARY TUBERCULOSIS

Anatomical Diagnosis. Chronic genito-urinary tuberculosis;  
Chronic tuberculosis of right pleuræ; Chronic fibrous pleuritis;  
Acute general miliary tuberculosis.

Male, white, age thirty-seven years. The body of medium size, strongly built, fairly well nourished. Surface smooth, no œdema. Rigor mortis marked. Slight post-mortem congestion. Subcutaneous fat in medium amount, muscles red.

Peritoneum smooth. The mucous membrane of pharynx, larynx and trachea congested. Heart weighs 310 grams. Pericardium normal. Valves and myocardium normal.

Mucous membrane and bronchi strongly congested. Both lungs are adherent to pleura. On the left side just above the diaphragm, where the lung is densely adherent, the pleura is greatly thickened with caseous material between the layers. Both lungs everywhere contain miliary tubercles, homogeneously distributed. At various places in the left lung close beneath the pleura there are areas of recent hæmorrhage extending a short distance into the pulmonary tissue. In the right lung at the lower border there is an area of caseation which has the general configuration of an infarct. Along the upper edge of the lower lobe there is a similar dry caseous area, triangular in shape. All the blood vessels of the lung opened, and in neither arteries nor veins are any tubercles found.

The liver weighs 1620 grams. Rather pale. On the surface and on section miliary tubercles can be discerned.

The spleen weighs 265 grams. The capsule wrinkled. On section filled with miliary tubercles.

The capsule of the left kidney easily strips off. Throughout this kidney both in the cortex and pyramids there are numerous large tubercles, many of them apparently conglomerate, others single. The pelvis of the kidney and ureter smooth. The right kidney is small, weight 110 grams. The capsule adherent. On section, in places, the entire pyramidal portion of kidney is destroyed and the calices converted into tuberculous sacs, which extend to within a few millimeters of the surface. In other places the pyramids are converted into a soft, easily broken-down caseous tuberculous mass. The pelvis is thickened, the surface caseous. The right ureter for its entire distance shows the same change as the pelvis, being covered everywhere with caseous tissue in and beneath which are miliary tubercles. In the bladder around the entrance of the ureter there is an extensive surface loss of tissue and at the bases

of these erosions there are innumerable small projecting miliary tubercles.

On both sides the epididymes are enlarged, and indurated and contain large, firm, caseous areas. This condition is more marked on the right than on the left side. This caseation on the right side extends into the tissue of the spermatic cord, the vasa deferentia being converted into a hard caseous fibre throughout the entire length of the cord. The seminal vesicles on both sides are tuberculous. On the right it is enlarged and solidified, the lumen being filled with caseous material. The mucous membrane of the stomach and intestines normal. Pancreas and adrenals normal. All of the lymph glands are enlarged and contain miliary tubercles. Examination of the thoracic duct negative.

Aorta smooth with the exception of a few scattered miliary tubercles along the intima.

**REMARKS.** In this case it is difficult to ascertain the seat of the primary infection. The tuberculosis of the genito-urinary system is apparently the oldest focus in the body although the large caseous area of the right pleura is also old. It is impossible to say whether the genito-urinary tuberculosis was an ascending or descending infection. From some one of the chronic lesions the tubercle bacilli have gained entrance into the blood, this resulting in the widespread miliary tuberculosis. In many such cases it is possible to trace the point at which the tubercle bacilli gain entrance into the blood, but in this case it was not possible.

#### A CASE OF TUBERCULOUS PHTHISIS WITH AMYLOID DEGENERATION OF ISLANDS OF LANGERHANS AND DIABETES MELLITUS

**Anatomical Diagnoses.** Diabetes mellitus; Glycogenic degeneration of tubules of Henly; Tuberculosis of lung with cavity formation; Miliary and conglomerate tubercles in lung; Caseous tuberculous pneumonia; Chronic fibrous pleuritis; General arterio-sclerosis; General amyloid degeneration; Granular ependymitis.

Male, white, age forty-three years. Body well developed, poorly nourished, rigor mortis present. Slight livores mortis. No œdema. Subcutaneous fat small in amount, muscles dark red. Peritoneum smooth, no exudation. Diaphragm at fifth rib on right side, at the lower border of the fourth rib on the left. Both pleural cavities completely obliterated by firm adhesions.

Pericardial cavity negative. Heart weight 350 grams. Myocardium normal. Along the coronary arteries there are small, white, circumscribed areas of sclerosis. On sections of the artery through such an area, the sclerosis is lateral only, and the artery at the point slightly narrowed.

Lungs. Each apex is occupied by a cavity into which several bronchi open. The cavity at the apex of the right lung is 4-5 cm. in diameter and contains opaque, yellow, tenacious, necrotic masses attached to the wall. The wall of the cavity extends irregularly into the surrounding lung tissue, which is for the most part solid and caseous. The necrotic tissue of the wall is bathed in gray, thin, gruel-like fluid containing yellowish specks, which, on examination, are composed of masses of tubercle bacilli. The cavity in left lung occupies the upper and outer half of the upper lobe. In places the outer wall is 1-3 mm. in thickness and consists of the thickened pleura lined on the inside with granulation tissue. Large masses of soft, opaque, yellow, necrotic tissue are attached to the wall. The surface beneath pleura shows numerous depressions with necrotic caseous tissue between. Contents of the cavity same as in left lung. In each upper lobe the tissue about the cavity is in part distinctly caseous, in part tough, resistant, and of a slaty color. Embedded in this are many firm, gray or yellowish-gray nodules (tubercles) 1-5 mm. in diameter, the larger suggesting a conglomerate composition. Disseminated through the middle and lower lobes of the right lung and sparsely scattered in the lower lobe of the left are a few fine, pearly tubercles and firm conglomerate tubercles 2-5 mm. in diameter. Peribronchial lymph nodes are enlarged and caseous.

Spleen weight 200 grams. Capsule thin, slightly wrinkled. Organ lax and soft. Malpighian bodies small. Pulp is pale red. The trabeculae are visible.

Liver, weight 1690 grams. Lobules visible, centres often slightly injected.

Gall bladder and ducts normal.

Pancreas normal.

Kidneys, weight 440 grams. Capsule easily stripped from a smooth gray surface of a yellow tint. The cortex on section pale and opaque, varying from 1-0.3 cm. thickness. Glomeruli not visible. Pyramids pale, contrasting slightly with cortex.

The aorta shows a few yellowish-gray elevated plaques 1-4 cm. in diameter. Behind the aortic cusps is a circular yellowish zone of sclerosis 1 cm. wide; the intima over all these areas is smooth.

The weight of brain 1540 grams. The meninges normal. Over the floor of the fourth ventricle there are a number of minute gray elevations so close together as to give a fine roughening of the surface.

Middle ears normal.

Microscopical examination of pancreas shows amyloid infiltration of the walls of the smaller arteries and extending from here to some extent into the surrounding tissue. The amyloid is chiefly marked in the Islands of Langerhans which are, for the most part, converted into amyloid masses. The kidneys show marked amyloid of glomeruli, of glomerular arteries and of the straight vessels of the pyramids. The epithelium of the proximal convoluted tubules is swollen and contains hyalin globules. The epithelium of Henly's loops is greatly swollen and vacuolated. Iodine staining after hardening in absolute alcohol shows in these apparent vacuoles, hyalin masses (glycogen) staining with iodine.

REMARKS. A case of chronic tuberculosis of lungs with resulting amyloid. Amyloid degeneration of Islands of Langerhans resulting in diabetes, has been followed by rapid extension of the tuberculosis in the lung; this is shown by the extensive necrosis and caseation and softening, large masses of caseous necrotic lung tissue being still adherent to the wall of the cavity. It is very probable that in this case the extension of the process in the lung was assisted by a mixed infection with the pyogenic cocci. In diabetes, infection is facilitated and infectious processes of all sorts extend more rapidly.

## LEPROSY BACILLUS.

This is a slender, often slightly curved bacillus, presenting much similarity both in morphology and in staining reaction to the tubercle bacillus. It can be isolated and grown on special culture media and after several generations it grows on ordinary media. The organism is pathogenic for Japanese waltzing mice and for monkeys, in which it produces fairly characteristic nodular lesions.

In man the disease appears in two well-marked forms, the nodular or tubercular and the anæsthetic. In the nodular form large and small circumscribed nodules appear in the subcutaneous tissue, preferably on the forehead. The nodules are in the corium, the fibres of which are separated by masses of endothelial cells which appear in two forms, as large cells resembling large phagocytic cells and as large vacuolated masses. The vacuoles in these cells are filled with fat. In both sorts of cells there are great numbers of leprosy bacilli which in the vacuolated cells surround the vacuoles. There also are large globular masses which by some are regarded as cells, by others as thrombosed lymphatics which are filled with bacilli. Lesions very similar to those of the skin, but associated with ulceration, may be found in the mucous membrane of the nose. The lymph nodes are but little enlarged and the sinuses contain numbers of the large vacuolated cells filled with bacilli. Similar cells may be found in the liver and spleen. The source of the fat in these cells is uncertain, since the bacilli themselves produce a fatty substance which stains with osmic acid.

In the anæsthetic form of leprosy there are lesions in the nerves and spinal cord. The nerves, the interstitial tissue and even the ganglion cells of the cord may contain great numbers of bacilli. Neither caseation nor necrosis is associated with the action of the leprosy bacilli in the human body and they produce little or no inflammatory reaction in the tissue about them. The organism must be regarded as one with very little virulence but with great power of proliferation. Secondary infection, especially with tuberculosis, is a frequent cause of death.

## TREPONEMA PALLIDUM.

This is a thin, threadlike organism of corkscrew shape, varying in length from 4-14  $\mu$ . The curves are acute, symmetrical, and, according to the length of the organisms, vary in number from 4 to 20. The organism is actively motile and may be demonstrated by various methods of staining, the best being by silver impregnation.

**OCCURRENCE OF ORGANISMS.** The organisms are found, often in great numbers, in all the acute lesions of syphilis and in no other disease. In anthropoid apes lesions of the same character as the human disease and containing the treponemata are produced by inoculation with disease products containing the organisms. In the lower apes the primary lesions without secondary are produced and, to a certain extent, infections are produced in rabbits. Under natural conditions, the disease is exclusively one of man. The relation of the organism to the disease is further shown by the fact that infections by pure cultures have produced the disease in monkeys and by the immunological reactions.

**PERIODS OF DISEASE.** The pathology of the disease can be divided into three periods which are separated from one another by varying intervals of time; in different cases the lesions, in location and character, vary with the periods, but show a general interrelation. The primary infection is most frequent on the skin of the genitalia; it is rare in other places, and its occurrence is favored by a surface lesion. At this point there is formed, slowly and without pain, a hard papule which slowly increases in size; this becomes a shallow ulcer which produces a small amount of thin exudate. In certain cases the ulcer is preceded by a vesicle. The extreme induration and the circumscribed character of the lesions are the most prominent features. Microscopically, there is an intense diffuse infiltration, chiefly with lymphoid cells below the surface, and lower down the infiltration is localized around the vessels. Between these foci of cell infiltration there is proliferation of the connective tissue. The walls of the vessels and especially the walls of the small veins often show not only an infiltration of the tissue about them, but a growth of the intima which leads to a



diminution of the lumen. In the cellular infiltration epithelioid and giant cells may be found. After healing an indurated cicatrix remains. During the development of the lesion, extension of the infection by the lymphatics occurs, which is shown by a slowly developing enlargement and induration of the regional lymph nodes. At the same time the virus passes into the blood and further foci of infection develop, characteristic of the secondary period. All the lymph nodes of the body are swollen, indurated and painless. There is a skin eruption which takes various forms, most frequently appearing as a roseola. In this same period lesions develop on the mucous membrane consisting of areas of hypertrophy of the papillæ, *broad condylomata*. The swelling is due to infiltration, chiefly of lymphocytes and plasma cells, around the dilated lymph and blood vessels of the upper layers of the mucosa, together with proliferation of the endothelium. There may be jaundice at this period, which can be referred to similar processes about the bile ducts, and anæmia due to the destruction of the red blood corpuscles. The lesions in the tertiary stage consist of two sorts, one of diffuse chronic interstitial inflammations, which in their histological appearance present nothing characteristic of syphilis, and are apparently due to the effect of the toxin in the blood; in the other form there are produced circumscribed nodules which are known as *gummata*. In these there is formation of granulation tissue which has a special tendency to fatty degeneration and to caseation. When of recent formation the gummata appear as gelatinous or firm masses of granulation tissue with yellow foci. In a later period they often show circumscribed and firm islands of caseation in a white cicatricial tissue. The gummata may form large tumor-like masses, or they may appear as microscopic structures, as masses chiefly of lymphoid cells, disposed to necrosis. The granulation tissue of the gummata is especially rich in lymphocytes, fibroblasts and giant cells frequently are present. With the removal of the cells and the cessation of the process, the gummata heal, leaving deep cicatrices which may become adherent to neighboring organs. Ulceration and destruction of tissue can be very extensive, and may affect the bones, and in the nose may destroy the support of the nasal bones producing the so-called saddle nose. The caseation develops more slowly, the foci are more circumscribed and firmer than is the caseous tissue of the tubercle. Around the

periphery the connective tissue extends in radiating lines into the surrounding tissue. Such gummata frequently are seen in internal organs, particularly the liver. In those developing in the subcutaneous tissue and in the periosteum the cellular infiltration is more extensive, there is a greater tendency to fatty degeneration of the cells, and large endothelial cells filled with fat accumulate around them. The process often is complicated by suppuration due to pyogenic infections. Cicatrices resulting from ulceration can lead to extensive stenosis as in the larynx, in the trachea, or in the intestines. There are a great number of pathological conditions of the central nervous system produced by syphilis, in part focal and due either to direct action of the organisms or to results of arterial disease, in part consisting in degenerations of nerve tracts due to toxic action. Amyloid disease frequently is caused by syphilis. Although the association of many of these lesions with syphilis has been definitely established, still the anatomical diagnosis of syphilis in this late stage cannot be made with certainty without the demonstration of the treponema in the lesions. Probably the most characteristic lesion in syphilis is the implication of the vessels in the pathological process, a condition found in all the stages of the disease. In the early lesions there are acute processes around and within the vessels in the foci, and in the late stages lesions, not only in the vessels in the foci, but also occurring independently. The small arteries of the base of the brain are a place of predilection for syphilitic changes. The difference between the syphilitic changes and the ordinary arterio-sclerotic changes in these vessels lies in the absence of calcification and macroscopical necrosis. Microscopically, there is cellular infiltration in the adventitia which extends into the surrounding tissue of the meninges, and growth of the intima producing narrowing or occlusion of the lumen. The internal growth may be concentric or more marked on one side, and the degenerative changes in the media, which are so marked in nonsyphilitic arterio-sclerosis, are absent. The process may be associated with thrombosis. The changes in the larger arteries which frequently lead to aneurysm have been considered.

Congenital infection of the embryo or foetus is frequent, and, in certain stages of disease in the mother, constant. The foetus frequently dies before delivery and the surface epidermis becomes

macerated. In this syphilis of the newborn the lesions have the general character of late syphilis and a few or many organs may be affected. There is no primary lesion. Interstitial changes are more prevalent than gummata. The gummata may appear as miliary or larger nodules. The most frequent condition is swelling of the spleen and the condition known as osteo-chondritis syphilitica, which appears at the diaphyso-epiphyseal junction as a yellow uneven line, at which point separation of the epiphysis easily takes place. The skin shows papullar and pustular lesions. There are often bullæ on the palms of the hands and the soles of the feet. In the lungs there is often a syphilitic process which takes the form of gummata and also so-called "white pneumonia." The gummata are yellowish or grayish white, are not sharply circumscribed, and usually are situated beneath the pleura. In the areas of white pneumonia the lung is firm and white or pale red in color. The alveolar walls are greatly thickened and the contracted air spaces filled with desquamated epithelium and leucocytes. In congenital syphilis there usually are lesions in the adrenal glands and pancreas consisting in fresh inflammatory cell foci with necrosis. Both gummata and interstitial lesions are found in the liver. In syphilis of the placenta the villi are thickened, infiltrated with cells and often necrotic. Ascites and general dropsy are not infrequent. The organisms are especially abundant in congenital syphilis, being found in all organs and tissues and often in enormous numbers. They have a special tendency to lie in the walls of vessels and in the tissue spaces about them. In the connective tissue spaces their long axis is in the direction of the fibres. In the skin lesions they often are found in great numbers between the epithelial cells. They rarely are found within the cells. They may be found in great numbers in organs in which the syphilitic changes are marked, and in other cases they are found in the largest numbers in organs which show little or no alteration and are few or absent in organs most affected, seemingly disappearing with the advent of the tissue reaction. In cases of tertiary syphilis the parasites are infrequent, but they have been found in syphilitic arteritis, in syphilitic endocarditis, in the tertiary syphilis of the skin, and in fresh gummata.

**SYPHILITIC LESIONS IN GENERAL** are characterized by their painlessness. This is due in part to their slow development and in part to the fact that the nerves in the part become degenerated. Exuda-

tion as a rule plays but little part in the formation of the lesions. The organisms do not attract polynuclear leucocytes. They have, however, been occasionally found within them. Leucocytes take part in the production of the lesions only when there is associated necrosis. The syphilitic organism does not tend to the production of severe destructive lesions in the tissue. It has the power of active proliferation, but the tissues have a high degree of immunity toward it. With a little less virulence on the part of the organism, a condition closely akin to a symbiosis might be established. The organism appears to have a similar high resistance towards the many defensive factors in the body.

**IMMUNOLOGICAL STUDY.** The difficulty of experimentation in the disease has rendered immunological investigations difficult. In spite of this fact, however, two approximately specific reactions have been developed. The first, the so-called Wassermann reaction, is almost absolutely specific and depends upon the fact that there is developed in the blood of the patient a substance which, in the presence of a lipoid substance obtained principally from the livers of congenitally syphilitic infants (also from guinea pig hearts and from various other normal organs), serves to fix or bind complement so that it cannot complete a hæmolytic system. The second, the so-called luetin reaction, depends upon the fact that an intracutaneous injection of an extract of pure culture of *treponema pallidum* produces, in the syphilitic patient, a wheal or circumscribed inflammatory area. The luetin reaction, as yet, is not so firmly established as a diagnostic measure as is the Wassermann reaction.

#### A CASE OF ACUTE AND CHRONIC MITRAL ENDOCARDITIS ASSOCIATED WITH NUMEROUS OTHER LESIONS AND INFECTIONS.

**Anatomical Diagnoses.** Syphilis; Acute and chronic mitral endocarditis with stenosis; Hypertrophy of heart; Arterio-sclerosis of aorta; Miliary aneurysms and thrombosis of cerebral arteries; Amyloid degeneration; Cirrhosis of liver; Strictures of urethra; Operation wound in perineum with opening into urethra; False passage in urethra; Chronic urethritis; Hypertrophy of bladder with cystitis; Purulent infiltration of prostate; Chronic inflammation of seminal vesicles with atrophy; Acute pyelonephritis; Chronic interstitial orchitis; Operation wound in mastoid; Acute

mastoiditis and otitis media; Acute broncho-pneumonia; Chronic fibrous pleuritis; Chronic fibrous peritonitis; Streptococcus and colon bacillus infection; Streptococcus septicæmia.

Male, negro, age thirty-five years. One operation had been performed in order to open and drain the infected mastoid cells and another to provide an opening in the urethra which had become closed by stricture.

Autopsy seven hours post mortem. Body well developed, well nourished and muscular. Rigor mortis complete. No oedema. In the perineum is an open operation wound 3 cm. in length. Over the mastoid region on the left side is an operation wound lined with dark red granulation tissue which extends into the mastoid cavities. Subcutaneous fat well developed, muscles firm, dark red in color. Below the meatus the prepuce is adherent to the glans penis.

Peritoneum. The omentum is adherent to the abdominal wall at two points, to the right and left of the bladder. The spleen is adherent to diaphragm by masses of loose fibrous tissue, as is also the right lobe of the liver. There are many depressed, irregularly stellate, opaque, white thickenings of the capsule of the liver. The mesenteric lymph nodes are prominent and on section firm with pale centres.

Pleuræ. Left lung at the apex and over the entire base is adherent by firm fibrous adhesions. The right is similarly adherent at the apex, posterior border and edges of base.

Pericardial cavity contains a small amount of clear fluid; no adhesions.

Heart weight 510 grams. It is large and distended with liquid blood which clots on removal. The myocardium is firm, the wall of the right ventricle hypertrophied. Valves of right side of heart are normal. The mitral valve segments are thickened and adherent by cartilage-like tissue at their junction on the right side. The anterior segment of the valve is calcified near its attachment and the auricular surface is partly covered with translucent, opaque yellow vegetations some of which are easily detached. The free edge of the posterior segment is thickened and the auricular surface contains a few nodular vegetations. The chordæ tendineæ are thickened and contracted. The wall of the left auricle is slightly thickened, the endocardium rather opaque. The coronary arteries are normal.

Arteries. In the ascending portion and arch of the aorta there are several large areas of sclerosis almost encircling the artery. These areas are elevated from 1-2 mm., the surface irregular; in some the centre is lower than the elevated edges. On section the entire thickness of the wall shows a gray opaque tissue with no clear separation of intima from media. The entire artery at this point is somewhat dilated, measuring

9 cm. There is a similar large white elevated area midway between the cœliac axis and the bifurcation. There is no calcification. The other arteries in the body appear normal.

**Lungs.** The anterior borders of both lungs are emphysematous. In the upper and middle lobe of the right lung there are a few red granular areas of solidification around the bronchi, a very few similar areas in the left lung. A muco-purulent fluid can be expressed from the bronchi. The posterior portions of both lungs are congested and œdematous.

**Spleen** is large, weight 200 grams. It is firm, dark red in color. On section the surface is dark red with small rather pale homogeneous refractive areas. The malpighian bodies not prominent; trabeculæ visible.

**Liver**, weight 1700 grams. All surfaces show irregular linear and stellate thickenings of the capsule with grayish cicatricial tissue extending from these into the liver. On section red with pale areas, but no distinct nutmeg appearance. The consistency is somewhat increased. The gall bladder and ducts are normal.

**Gastro-intestinal tract.** Mucosa somewhat injected, otherwise normal.

**Pancreas** normal.

**Kidneys** large, weight 550 grams. On section cortex enlarged and contains pale opaque yellow areas and lines extending from pyramids.

**Adrenal glands** normal.

**Testicles.** The cavity of the tunica vaginalis is obliterated on both sides. The vasa deferentia are converted into solid white fibrous structures. The left testicle is small and contains a yellowish translucent mass 0.5 by 1 cm. in diameter. The remainder of the testicle is hard and the tubules do not thread. The right testicle is small, firm, white, the parenchyma seemingly reduced.

**Bladder.** The walls thickened. The mucosa contains dark blue black areas of hemorrhagic extravasation from one to several millimeters in diameter. Prostate enlarged and indurated. Pus exudes from lower portion on section.

**Vesiculæ seminales** have small irregular cavities with thickened pigmented walls. They are surrounded by dense yellowish fibrous tissue, and form large divergent masses behind the bladder.

**Urethra.** Posterior to entrance of the operation wound which is 3 cm. from the bladder the lumen is obliterated and there is a false passage leading into the bladder. The surrounding tissue is fibrous and contracted. Throughout its course the mucosa of the urethra and the tissue about it is thickened; 2 cm. from the meatus there is a definite constriction of the urethra for a distance of 2 cm.

**Bone marrow.** That of femur shows some increase of red marrow.

Head. Skull thick, sinuses and dura normal. There is some clouding in the pia arachnoid but no exudate. Vessels at base of brain normal. No macroscopic lesion of brain save numerous small transparent granulations on surface of ventricles and a number of small red points (apparently dilated vessels) in the underlying brain tissue.

The left middle ear is filled with pus, smears from which show large numbers of streptococci.

The spleen and kidneys on addition of iodine give the amyloid reaction.

Both cultures and smears from the foci of suppuration in the kidneys give colon bacilli. Cultures from heart blood gave abundant colonies of streptococci.

Microscopic examination of the foci of broncho-pneumonia show the bronchi filled with pus and in the surrounding alveoli fibrino-purulent exudation. There is considerable oedema of the peribronchial tissue and infiltration with polynuclear leucocytes, lymphoid and endothelial cells. In the purulent exudate in the bronchi there are short chains of streptococci and within the cells numerous diplococci. The testicles show well marked increase in the interstitial tissue with atrophy of tubules. The nodular area in the left testicle is composed of dense connective tissue with no traces of tubules within it.

The kidneys show foci of purulent infiltration extending throughout cortex. Pus cells in large numbers are contained in the tubules. The glomeruli are enlarged and show hyalin masses (amyloid) along the capillaries.

The follicles of the spleen are slightly enlarged and contain foci of amyloid.

In the liver the connective tissue along many of the portal spaces is increased in amount and infiltrated with cells. The condition varies greatly in different parts. The central veins and capillaries are dilated and the liver cells between them atrophied.

A section of the lateral ventricle of the brain shows the small granules on the surface to be composed of neuroglia tissue. The section passed through several of the red points noticed and shows these to be due to aneurysm formation. The wall of the dilated vessel is hyalin, and presses upon the surrounding brain tissue, the perivascular space being obliterated. In several of the arteries in the section there is a similar degeneration of the wall and a formation of small mural thrombi.

**REMARKS.** The case offers a singular variety of lesions, most of them due to past and present infectious processes. The chronic fibrous peritonitis and pleuritis call for no special consideration. The lesions in the genito-urinary system can be taken together.

There has been a primary and long enduring gonorrheal infection which has produced the chronic urethritis and strictures, and by extension to the epididymes, testicles and seminal vesicles, atrophy, destruction and chronic induration of these structures. (The possible influence of syphilis in their causation cannot, however, be excluded.) The operation in the perineum was performed to open the constricted urethra. The hypertrophy of the bladder was the result of the increased muscular effort necessary to discharge its contents through the constricted urethral canal. The cystitis may have existed prior to the operation or may have been produced by a subsequent infection. Infection easily occurs in such cases. The infection extended into the prostate and along the ureters into the kidneys. This condition of acute suppurative nephritis in association with acute cystitis is not uncommon. It is not necessary to assume that the organisms actually travel up the ureter, but the infection extends by continuity of the infected fluid. The chronic and acute endocarditis may represent a separate infection or it may have been due to the gonorrheal infection. This has led to hypertrophy of the right side of the heart and to general passive congestion which was not sufficiently marked to have produced oedema. The diagnosis of syphilis, although probable, must in the absence of clinical history, Wassermann test and the formation of definite gummata, remain uncertain. In its favor are the amyloid degeneration, the character of the arterio-sclerosis in the aorta, the coarse bands of connective tissue in the liver and the extensive interstitial changes and atrophy in the testicles. The last would have been more characteristic of syphilis had the testicles alone been affected without involvement of the rest of the genito-urinary system. The miliary aneurysms of the brain may have been due to degeneration of the arterial walls caused by syphilis, although no morphological or statistical evidence of the association has been adduced. The acute otitis media and the mastoiditis for which an operation had been performed were probably due to infection of the middle ear extending from the throat. Streptococci were found in the pus from the middle ear. The foci of broncho-pneumonia are due to infection with streptococci and pneumococci, these entering into the lung by the bronchi. A terminal streptococcus septicæmia is not uncommon. The organisms may have been carried into the blood from several foci.



## STREPTOTHRIX ACTINOMYCES (ACTINOMYCES BOVIS)

This is an organism belonging to the trichomycetes or filamentous branching bacteria. In the tissues the masses of organisms appear as pale yellow granules, 1 mm. or more in size. Microscopic examination shows the periphery of the granules to be composed of radiating club or pear-shaped bodies closely set together, to which appearance is due the name "ray fungus." In association with these bodies or independently, branching filaments are found.

Infection in man occurs in the alimentary canal leading to the formation of large tumor-like masses of granulation tissue, in the interior of which are found foci of suppuration around masses of the organisms. The infection often occurs in the jaws and around the teeth, and secondary foci may form in the internal organs.

### A CASE OF ACTINOMYCOSIS

(Only that part of the autopsy which has immediate reference to the lesions is quoted.)

**Anatomical Diagnoses.** Actinomycosis (primary in right inferior maxilla with extensions in the subcutaneous tissue of face and neck, into the temporal bone and into brain producing multiple abscesses); Metastases in liver.

White, male, age fifty-two years. The entire right side of face and neck is greatly swollen, indurated and below the angle of the jaw, are three discharging sinuses with retracted, indurated margins. In the subcutaneous tissue on this side of the neck are numerous foci of pus varying in size from 0.2-1 cm. in diameter and embedded in extremely dense, pearly gray tissue. The pus contains yellow firm granules, smears from which show Gram staining, branching filaments. There is a small blue red tumor mass 1 cm. in diameter projecting from the inner surface of the gum at the base of the left inferior canine tooth. Upon removing the tissue from the right temporal region, the bone is bare, soft and necrotic.

The dura is closely adherent to bone beneath the temporal fossa. It is attached to the pia-arachnoid over the inferior portion of the right temporal lobe, but is free elsewhere. The cerebral sulci are shallow, the

cerebral surface unusually smooth. The right temporal lobe of the brain is enlarged. On section it contains a large pocket of green semifluid pus, and in the vicinity of this there are several smaller abscesses. The wall of the large abscess has a tough lining membrane in which are visible some small yellow tubercles. The odor of the abscess contents is very offensive. Both lateral ventricles are slightly dilated. Section of basal nuclei shows a small hæmorrhage on the right side external to and just below the lenticular nucleus. This hæmorrhage is 1 cm. in diameter and reaches the inner margin of one of the smaller abscesses in the right temporal lobe. In the right middle fossa of the skull are two small perforations of the squamous portion of the temporal bone which communicates directly with a small subcutaneous abscess in the right temporal fossa. The larger abscess in the temporal lobe is immediately over this region. The adjoining bone is roughened and necrotic.

The weight of the liver is 1500 grams. On the diaphragmatic surface of the right lobe there is a slightly elevated, yellow-white area 2 cm. in diameter extending a distance of 2 cm. into the hepatic substance. On section this nodule is firm, gray, with minute yellow foci 1 mm. in diameter within its substance. The liver otherwise normal.

On microscopical examination of the tissues, numerous masses of the organism were found everywhere. They lay within pus pockets in the midst of a dense cicatricial connective tissue.

**REMARKS.** The case illustrates the great tendency of the infection to extend locally along the surface of bone. The infection probably began in a tooth in the alveolar process of the lower jaw and from this extended over the body and the ascending ramus to the base of the skull producing necrosis and perforation followed by hemorrhage and abscess in the brain. The metastases in the liver is by means of the blood vessels.

## BACILLUS MALLEI

The glanders bacillus is a small rod with rounded ends and is somewhat variable in length. It produces no spores, has no flagella, and is decolorized by the Gram stain. The organism is pathogenic for guinea pigs and rabbits. Inoculation of guinea pigs, either subcutaneously or in the peritoneal cavity, produces a characteristic acute swelling and inflammation of the testicle. In man the disease is not infrequent, the infection almost invariably being acquired from the horse. It appears in the acute and chronic form, the lesions in man having much similarity to the same forms of disease in horses. In the chronic form the infection may persist for years, producing repeated abscesses, usually in the muscles. The lesions consist in inflammation with purulent exudation and softening, there being a marked tendency to destruction of nuclei and formation of nuclear detritus. Large endothelial giant cells not uncommonly are present. The bacilli exert their action by an endotoxin which may be obtained from the dead bacilli.

### A CASE OF ACUTE GLANDERS IN MAN \*

Anatomical Diagnoses. Glanders; Hæmorrhage, ulceration and pustule formation in skin; Abscesses in muscles and in lungs; Acute pleurisy; Acute parenchymatous degeneration.

White male, age thirty years. Clinical history. On September 30th, while skinning a horse which had died of glanders, he cut his finger. The next day the finger pained him but did not appear to be injured. Eight days later he was seen by a physician who incised the finger. He remained in bed complaining of fever with great thirst until October 24th, when he was admitted into the hospital and the finger was amputated. On the fourth day after admission, pustules appeared on the forehead and upon other parts of the body. Later those on the forehead became confluent and ulcerated. Death occurred November 1st.

Autopsy five hours after death. The body is that of a well-built, muscular man. Subcutaneous fat moderate in amount. Rigor mortis very marked. Slight lividity of dependent portions. Amputation of finger.

\* J. H. Wright, Journal of Experimental Medicine.

The skin of the forehead as low as the eyebrows and of the scalp as far back as the vertex is thickened, discolored, eroded, and feels dense to the touch. The margin of this area is scalloped, and is rather sharply elevated above the adjoining normal skin. In color it is purple, mottled with small yellow areas. Over the upper portion of the forehead and at the beginning of the scalp, the epidermis is purple to black in color, and more or less detached from the underlying tissue, from which it can easily be removed. In places it is lacking, leaving irregular and rather superficial ulcerations, in which there can be made out many yellow specks, not soft enough to be called pus. On section the tissue is deeply infiltrated with an opaque, yellowish-white material, which is rather firm, and can not be squeezed out like pus. In the left upper eyelid are several pustules, single and grouped. Over the zygomatic arch and on the right side there are also two small groups of pustules. In the skin of the left arm, on its outer and posterior surfaces, are scattered several pustules from 1-3 mm. in diameter and about 1 mm. in elevation. Three or four similar pustules are seen on the skin of the right arm, and one on the skin over the tibia. On the front of the chest are two pustules, besides a small group below the outer end of the left clavicle. The pustules found in these situations generally present a purplish tint about their bases. In the pectoral muscles on the right side, near the sternoclavicular articulation, is a small, oval, yellow, semi-solid nodule about the size of a split pea. The left axilla contains an area of suppuration in the axillary fatty tissue about 5 cm. long and 3 cm. in diameter. On section, this area resembles a bit of very coarse sponge, the meshes of which are filled with a thin, odorless, yellowish fluid. Some of the lymph nodes in the neighborhood are still well preserved, although considerably enlarged, and on section they show a yellow infiltration on the side toward the pus.

**Lungs.** The left lung over the upper lobe is bound down by fibrous adhesions. The right lung is free. Both are moderately congested, and slightly oedematous posteriorly. On the lower surface of the right upper lobe are two yellow, elevated areas, 2 mm. in diameter, surrounded by a dark red zone. The pleura over both areas is covered with a thin coat of fibrin. Scattered through the remainder of the right lung, usually just beneath the pleura, are in all about a dozen small resistant areas, the largest not more than 1 cm. in diameter. On section, some of these areas are found to be solid, of a dark red color, with yellow points; others softened or broken down, forming abscesses or cavities filled with fluid of a purulent character. On the pleura over these areas there is in many places a thin fibrinous exudate.

**Heart.** Not remarkable.

Spleen. Enlarged to half again its normal size; soft. Follicles not visible on section.

Kidneys. Capsule very slightly adherent. On section, cortex more opaque than normal. Pyramids injected.

Liver. Slight cloudy swelling.

The deep cervical and mesenteric lymph nodes slightly enlarged and congested.

The nasal cavities and pharynx not examined.

Bacteriological Examination. Cover-glass preparations from the lesions on the scalp and from the pus of the axillary abscess show the presence of a few bacilli of medium size, with rounded ends, varying in length, and having faintly staining spaces in the protoplasm. The purulent-looking fluid from a small abscess cavity in the lung is negative on cover-glass examination. Cultures were made on coagulated blood serum (Löffler's mixture) in test tubes from the various lesions and from the organs and show glanders bacilli. Inoculation of guinea pigs with pure cultures give the usual lesions in the testicle.

**REMARKS.** The case is a simple one. A primary infection of the finger with metastases in the skin and muscles. The pustules in the skin which are produced in these acute cases may present some similarity to the pustules of smallpox and the diseases have been confounded. The resemblance is but superficial clinically and there is no histological similarity between the lesions of the two diseases. In the cutaneous pustules of glanders the epithelial lesions characteristic of smallpox are absent, the infiltration of the corium is more extensive and the lymphatic vessels are extensively involved in the process.

## BACILLUS ANTHRACIS

This is an organism of great medical interest because the first proof of the production of disease by bacteria was given in anthrax. The organism is a large bacillus staining easily with the ordinary bacterial stains and with Gram. It grows easily on the ordinary culture media at wide temperature limits, having saprophytic as well as parasitic growth. On artificial media the bacilli form long tangled threads. In the presence of oxygen it forms spores which are very resistant. It is highly infectious for white mice, rabbits and guinea pigs and produces one of the natural diseases of cattle. The synonym "milzbrand" or "splenic fever" has its origin in the constantly present acute swelling of the spleen.

The infection may be transmitted from animals to man, either from the carcasses or by handling hides or wool which contain the spores of the bacilli. Three types of the disease may be distinguished in man depending upon the locality of the infection. Anthrax of the skin appears in the form of the anthrax carbuncle and as an inflammatory oedema. The microscopic appearances in the carbuncle are characteristic. The bacilli appear in the greatest number in the upper layer of the corium and in the papillary bodies. There is an extensive and deep infiltration with fibrin, pus cells and red corpuscles, accompanied with necrosis. The organisms extend by the lymphatics to the adjacent lymph nodes and later into the blood, but the infection of the blood is not so common in man as in animals. Infection of the intestine produces large necrotic hæmorrhagic foci with great oedema of the surrounding tissue. Infection of the lung results from the inhalation of the spores (wool sorter's disease) and takes the form of large hæmorrhagic purulent foci.

## A CASE OF ANTHRAX IN MAN

**Anatomical Diagnoses.** Surgical wound of neck (removal of area of primary infection with bacillus anthracis); *Bacillus anthracis* septicæmia; Acute hæmorrhagic cerebrospinal meningitis; Acute focal hæmorrhagic enteritis; Acute mesenteric lymph noditis; Acute splenitis; Acute degeneration of heart, liver and kidneys; Bilateral hydrocele.

Patient white, age forty-seven years, a teamster employed in handling hides, entered hospital complaining of a painful swelling on the left side of neck. This appeared three days previously as a small red point and has rapidly increased in size. On the left side of the neck, in the middle, and a little posterior to the line of ear, is a hard, dark crust. The centre of the swelling is elevated 1 cm. above the neck level and extends over an area of 3 cm. The intense induration of the centre gives place to a slight œdema at the edges. Complains also of headache, loss of appetite and general discomfort. Temperature 103 degrees. The indurated area in the neck was removed. Patient died three days later in coma which followed delirium. A blood culture taken before death showed a pure growth of the bacillus anthracis averaging 180 colonies to 1 c.c. of blood.

Body is that of an exceptionally well developed, muscular, well nourished man. There is slight rigor mortis and post mortem congestion. There is no œdema; external orifices normal. On the left side of the neck in the middle there is an oval surgical wound 6 by 4 cm. In this area the skin and subcutaneous tissue has been removed, leaving a clean wound which extends downwards to the deep muscles of the neck. Around this wound there is slight œdema. Subcutaneous fat in fair amount, firm and yellow, the muscles of thorax and abdomen firm and dark red.

The peritoneum is smooth, pale and glistening, except for areas over two of the mesenteric lymph nodes and over a small swollen area on the mesentery and intestine 32 cm. from the ileo-cæcal valve. The peritoneum over the lymph nodes is slightly injected, and over the swollen area mentioned the intestine is deeply injected and cloudy. There are no peritoneal adhesions. The mesenteric lymph nodes are slightly swollen and reddish on section. There are two glands adjacent to the injected area of the intestine which are considerably swollen, 2 by 1 cm., and, on section, deep red, their centres soft. The tissue about them is injected.

Pleuræ. The lungs free from adhesions. Pleuræ smooth.

**Heart.** Pericardium contains a small amount of clear fluid. Weight of heart 412 grams. On section the myocardium is mottled with red and pale areas. The pale areas are irregularly distributed from 2-8 mm. in diameter, generally longitudinal in shape, corresponding to the direction of the muscle fibres. They are circumscribed and in them the myocardium is softer. The cardiac valves and coronary arteries are normal. The blood within the heart is fluid and is very dark in color. The left ventricle contracted 2 cm. in thickness, the right 6 mm.

**Lungs** are crepitant throughout. Both lower lobes, especially posterior portions, are congested, dark red in color, and on section a thin, blood-stained fluid escapes.

**Spleen.** Weight 350 grams. Capsule is smooth and glistening. On section a dark chocolate-brown, the markings and malpighian bodies indistinct. Pulp is soft and projects from the cut surface.

**Gastro-intestinal tract.** Stomach normal. In the ileum, 32 cm. from the cæcum, there is a swollen hæmorrhagic area 3 by 2 cm. in size corresponding to the swelling at the mesenteric attachment. Within the intestine at this point there is a dark red exudate. The remainder of the canal is normal.

**Pancreas** normal.

**Liver.** Weight 2040 grams. The capsule smooth. Pale brown in color. On section slight central congestion of the lobules.

**Kidneys.** Weight 462 grams. The cortex is 1 cm. in thickness, rather pale and opaque. Capsule strips easily. Markings normal.

**Adrenals** normal.

**Genitalia.** The tunicæ vaginales on both sides are distended with clear fluid. Testicles and epididymes normal.

**Mouth, throat, and organs of neck** normal.

**Brain, meninges and cord.** Scalp and calvarium normal. On removal of dura there is an abundant hæmorrhagic fibrinous exudation, in places 3 mm. in thickness, in the meshes of the pia arachnoid, which gives the appearance of a blood clot and extends over both lateral hemispheres and cerebellum and to a less extent over the pons and medulla. There is no exudation on the surface of the pia. On section of brain the exudate extends into the sulci and within the brain tissue there are numerous small punctate dark red areas most of which remain after wiping. In the ventricles a small amount of reddish fluid. The upper half of the spinal cord is surrounded by a subpial hæmorrhagic exudate, which is smaller in amount than that in the cerebral meninges and gradually fades out below. The vessels of cord are injected.

**Bacillus anthracis** found in smears of blood and in cultures from all organs.



Microscopic examination of the primary lesions shows infiltration of the entire area with a hæmorrhagic fibrino-purulent exudate. This lies in the corium, in the subcutaneous tissue and around the muscle fibres in the lower part of the section. Immediately beneath the epidermis the exudate is less marked and is more oedematous in character. The fibres of the corium appear as widely separated bundles. The fat tissue is destroyed, the fat cells not visible as such, but in their place are numerous round or oval clear spaces. The exudate varies somewhat in character; there are places where the tissue is filled with red blood corpuscles and in other places it contains chiefly polynuclear cells. All the blood vessels are widely dilated, there is mural arrangement of leucocytes and in the walls are emigrating leucocytes. In several of the veins and arteries there is active proliferation of the endothelial cells forming a thick cellular lining. Large bacilli are found in small numbers in the exudate and are more numerous just beneath the epidermis. Sections of the brain and meninges show a dense hæmorrhagic and fibrinous exudate infiltrating the arachnoid. In this there are widely dilated vessels. The exudate extends into the sulci and to some extent is seen in the perivascular spaces of the vessels entering the brain. Deeper in the brain there are foci of hæmorrhage in dilated perivascular spaces. The brain tissue around the exudate is oedematous. Bacilli in small numbers are found in the exudate.

Sections of the hæmorrhagic area in the intestine show an intense hæmorrhagic fibrinous exudate throughout the entire intestinal wall and extending into the attached mesentery. There is considerable necrosis of the mucous membrane with desquamation of epithelium.

The enlarged mesenteric lymph nodes show a hæmorrhagic infiltration with much fibrin in the dilated sinuses, with considerable necrosis and hæmorrhage in the follicles.

The spleen shows intense congestion and hæmorrhage. In the tissue there are large numbers of bacilli.

Heart, liver and kidneys show marked cloudy swelling and fatty degeneration, this latter being particularly marked in the heart.

**REMARKS.** A typical case of anthrax. The primary infection of neck probably resulted from carrying infected hides on the shoulders. There are secondary foci of infection in the meninges and in the alimentary canal and infection of the blood (septicæmia). The acute enlargement of the spleen is due to congestion and hæmorrhage and forms one of the most characteristic anatomical lesions of the disease. (Synonym: splenic fever.) The weight of the heart

is unusual, but in consideration of the occupation, which demands heavy labor, the size, muscular development and good nutrition of the individual, the rapid death and the acute degeneration should not be regarded as pathological. The same may be said of the increased weight of liver and kidneys.

The anthrax bacillus in the tissues produces necrosis with hæmorrhagic fibrinous exudation. In these lesions the necrosis of tissue is obscured by the exudate and in the primary lesion is shown only by the spaces occupied by the fat globules which have been freed by the destruction of the cells.

## BACILLUS DIPHTHERIÆ

Diphtheria is a typical toxic disease. The diphtheria bacilli are slender, straight or slightly curved rods, rarely of uniform thickness throughout. They may be club-shaped at one or both ends and occasionally are thickened at the centre. The organisms are easily stained and in certain cases appear to be traversed by transverse bands which give them a striped appearance. They produce no spores and are nonmotile. Growth takes place readily on most of the laboratory media, the most widely used medium being coagulated blood serum. The organism grows at temperatures varying between 19 and 42° C., and is probably an exclusive parasite. It is pathogenic for most of the laboratory animals. Infection in man takes place in the mucous membrane of the tonsils, uvula, pharynx; more rarely in the nasal passages and the larynx. The surfaces affected are covered with a gray, yellow-gray or brown membrane which adheres more or less firmly and when removed leaves a surface deprived of epithelium. When the membrane formation extends into the trachea it is easily removed and often separates subcutaneously in the form of a large cast. The membrane varies in structure in different places. It is composed chiefly of fibrin in the form of a meshwork with openings of various sizes, the long diameters of which are parallel to the surface. A variable number of degenerated leucocytes are enclosed in the fibrin. When the membrane forms over a thick squamous epithelium the epithelial cells take part in its structure. The cells undergo a hyalin change; the edges of the cells unite and form a reticulum in which the spaces represent the places formerly occupied by the nuclei. The fibrin on the surface is found in association with a fibrinous exudate which extends into the tissue. This often is combined with a hæmorrhagic exudation and extensive necrosis. The local lesions leading to membrane formation consist in necrosis of the surface and an inflammatory exudation in the tissue beneath, which, in contact with the necrotic cells, coagulates and produces the characteristic membrane. The bacilli have little or no tendency to invade, they grow in and on the surface of the membrane and produce there a

toxin which is absorbed and leads to degenerative changes in the internal organs. Toxic substances of the same character, as those produced by the bacilli when growing on the surface, are produced in culture media, and lesions similar in character to those of the internal organs produced by the disease may be produced in animals by injecting them with fluid cultures from which the bacilli have been removed by filtration. The bacilli occasionally invade the tissues and produce in them exudates of a fibrinous or purulent character. Beneath the membrane the tissue is hyperemic and there may be considerable exudation of a serous, fibrinous or hæmorrhagic character. There may be extensive necrosis of the glands or of the muscular tissue in the vicinity. The membrane may extend from the throat into the nose, into the Eustachian tube and middle ear. Other organisms, chiefly streptococci and staphylococci, may be found in large numbers in the membrane often exceeding the diphtheria bacilli in number. In fatal cases the lungs are almost invariably affected. The local infection may extend from the throat into the trachea and into the large and small bronchi producing a similar formation of membrane. The most common lesions found in the lung are areas of exudation into the bronchi and connecting air sacs. These areas vary in size from those just visible to those several centimeters in diameter and are more frequently seen in the inferior and posterior parts of the lung. The exudate is composed in most cases of fibrin, or it may be purulent or hæmorrhagic. Such foci of lung infection begin in the atria and from there extend into the air sacs. The larger areas are due, not to extension of the infection by continuity, but by infection of all of the terminal lobules of a single bronchial territory. The organisms producing these lesions of the lung may be diphtheria bacilli, streptococci, pneumococci and staphylococci, alone or in combination with one another. The cervical lymph nodes are enlarged, congested and softer than normal. All of the lymphoid tissue in the body is affected to a greater or less degree. The lymph sinuses are all enlarged and contain numbers of phagocytic endothelial cells and leucocytes. The cells in the germinal centres undergo necrosis and are replaced by large endothelial cells. The kidneys are nearly always fatty and the lesions are chiefly degenerative in character. In about one-fourth of the cases there is a condition known as acute interstitial nonsuppurative nephropathy.

This consists in the presence of foci in the interstitial tissue which are composed principally of plasma cells. In a smaller number of cases acute lesions of glomeruli are found. Degenerative changes are found in the heart, in the liver and in the nerves. The symptoms of the disease are referable rather to the action of toxins produced by the bacilli than to the local lesions associated with their presence, except where local obstruction, as in the larynx, may lead to death from suffocation.

#### A CASE OF DIPHTHERIA

**Anatomical Diagnoses.** Diphtheria with membrane formation in pharynx, larynx, trachea and bronchi; Tracheotomy; Bronchopneumonia; Acute parenchymatous degeneration; Streptococcus infection.

White, male, age seven years. Body that of a fairly well-developed and fairly well-nourished boy. Lividity of posterior portions of the body, no oedema, no rigor mortis. An open wound in the anterior middle line of the neck extending into the trachea. Subcutaneous fat small in amount.

Peritoneal surface smooth and glistening, intestines moderately distended.

Pleural cavities free from exudate or adhesions.

Pericardium and heart normal.

The organs of the neck with the lungs removed in mass. The œsophagus opened posteriorly. The mucous membrane of the mouth and pharynx intensely injected. On the right side covering the tonsil and extending to the pillars of the uvula and over the base of the tongue is a dirty brown or gray adherent membrane, not easily removed, coming away in small patches. The surface beneath is injected and rough. The membrane extends deeply into the crypts of the tonsil which is swollen and hæmorrhagic. On the left side over the swollen tonsil is a similar but less extensive membrane. The edges of the membrane are irregular. The trachea and larynx opened posteriorly. Beginning at the base of the epiglottis and extending throughout the larynx, trachea and large bronchi, there is a membranous exudate, white, soft, fragile, which can easily be stripped from the underlying deeply injected surface. There is an incision corresponding to the external wound which passes through the lower portion of the cricoid cartilage and the first and second rings of the trachea. The lymph nodes of the neck are enlarged, injected and soft.

The lungs collapse but slightly, the pleuræ are smooth, the surface mottled with red areas. On palpation there are distinctly perceptible smaller and larger firm areas. On section the lungs are hyperæmic and oedematous. Considerable blood and air-containing fluid escapes from incision. There are areas of consolidation from 0.5 to 1.5 cm. in diameter, some of these red, others dark, resembling infarcts. They are more numerous in the lower and posterior portions of the lungs, but the largest is in the upper lobe of the right lung. From some of the areas small drops of pus exude on pressure.

Spleen, enlarged, weight 165 grams. Capsule smooth. On section a deep red color, the markings obscure.

Pancreas and adrenals negative.

Liver, weight, 690 grams. Surface smooth, mottled with red and yellow areas.

Kidneys, weight, 135 grams. Capsule easily stripped, the surface smooth, foetal markings visible, cortex pale. Pyramids injected, markings obscure.

Genitalia, arteries and brain present no lesions. The middle ears normal.

Cultures from lungs show streptococci and diphtheria bacilli. No histological examination.

**REMARKS.** A typical case of severe diphtheria with secondary streptococcus infection. The character of membrane in pharynx and in trachea is characteristic. In the trachea easily removed, soft and easily torn; in the pharynx, the squamous epithelium of which enters into the membrane formation, tough, adherent. The congestion and hæmorrhage in the underlying tissue is also characteristic. The broncho-pneumonia is an invariable accompaniment of a diphtheria infection of this degree of severity and extension. The swelling of spleen and kidneys is due to acute degeneration brought about by the toxin. Histological examination shows necrosis in the lymphoid tissues.

## INFLUENZA BACILLUS

This is an extremely small bacillus  $0.5\ \mu$  long by  $0.2-0.3\ \mu$  broad, not motile, does not stain with Gram and produces no spores. It is cultivated with difficulty, hæmoglobin being necessary for its growth. It is not fatal for laboratory animals but intravenous injections in rabbits exert a toxic effect.

In man the organism occurs in a variety of pathological conditions, either alone or in association with other, and for the most part pyogenic, organisms. In cases of death from epidemic influenza the mucous membrane of the small bronchi is injected and covered with a muco-purulent exudate in which are great numbers of the bacilli. In addition to the bronchitis there may be extensive broncho-pneumonia, in the exudate of which the bacilli are found both free and enclosed in polynuclear cells. Cases of meningitis due to the influenza bacilli may occur both in the course of epidemics and sporadically. It also is frequently found in tuberculosis and other infections of the lung. In view of the frequency of the organism it is difficult to regard it as the essential cause of the great pandemics of influenza.

## TETANUS BACILLUS

This is a long slender organism possessing many flagellæ. It stains with usual bacterial stains and is Gram positive. It is a strict anaërobe and forms spores readily. It is found in cultivated earth and is a frequent if not constant inhabitant of the alimentary canal of horses. In cultures it forms a toxin to which its pathogenic action is due. Of all animals the horse is most susceptible to the action of the toxin. In man the disease is transmitted by wound infection. The inclusion of foreign bodies contaminated with bacilli in penetrating wounds favors infection, the bacilli finding favorable opportunity for development in the necrotic tissue around the foreign body. This type of wound tends to close on the surface thus providing an anaërobic culture medium.

Mixed infection may favor the development of the bacilli. The bacilli produce but slight local reaction of the tissue. The growth of the bacilli in the tissue is feeble, and their detection difficult. The infection atriun may be difficult to detect at the time when the effects of the toxin appear.



## BACILLUS PESTIS

This is a very short bacillus with rounded ends without motion, does not stain with Gram, forms no spores, retains vitality in darkness and in moist environment, grows readily upon meat infusion and at low temperatures. The organism is extremely pathogenic for the laboratory animals, particularly guinea pigs and rats, in which the mere rubbing of a culture on the unbroken skin is sufficient to convey invariably fatal infection. Man is very susceptible to the disease, infection taking place both by the skin and respiratory surface, the latter giving rise to the pneumonic form of the disease. Infection by the skin can take place through surface lesions, but the most common mode of infection is by the bites of fleas which convey the bacilli from infected rats. The bacilli, in great numbers, are found in the lymph nodes, in the spleen, in the liver, and in the blood. A common lesion in death from plague is the presence of hyalin thrombi in the glomerular capillaries.

### BACILLUS OF SOFT CHANCRE

This is a thick, short bacillus with round ends, having a tendency to form chains, non-motile, does not stain with Gram and does not grow on ordinary media. Infection in man takes place by coitus, the lesion appears on the genitals as an ulcer with sharply cut edges and a base covered with thin purulent and hæmorrhagic exudation. The edges are soft, there is always lymphangitis with inflammatory swelling and frequently suppuration of the adjacent lymph nodes.

## BACILLUS TYPHOSUS

This is a short, actively motile bacillus, having twelve or more flagella peripherally arranged. It is easily cultivated upon the usual laboratory media. It grows best at  $37.5^{\circ}\text{C}$ ., but also grows between  $15$  and  $41^{\circ}\text{C}$ . It is capable of both parasitic and saprophytic growth.

Infection takes place from the alimentary canal, but the site and the mode of infection are obscure. The lesions of the disease are most apparent in the lymphoid tissue of the alimentary canal and this has led to the view that the organisms enter the alimentary canal, multiply there and produce the lesions which constitute the focus of infection through which the further invasion of the body takes place. The process of infection seems to be that the bacilli enter the blood from the alimentary canal, possibly through an intact surface. During the somewhat indefinite period of incubation the bacilli multiply in the blood, and the characteristic lesions in the lymphoid tissue of the alimentary canal and elsewhere are due to the specific action of the bacilli and toxins on this tissue. The character of the lesions in the alimentary canal is due to the situation of the lymphoid tissue which facilitates surface necrosis and ulceration. The mode of action of the bacilli also is obscure. There seems to be little or no definite toxin produced in culture, but endotoxins have been obtained from the bodies of the bacteria. In the tissues the bacilli occur in groups in association with the lesions, and are not found within the cells. The fresher the autopsy, as a rule, the smaller the number of organisms which will be found. Growth of the single bacilli in the tissues takes place after death, resulting in the formation of the small clumps. The characteristic feature of the disease is the production, in enormous numbers, of large endothelial cells which have marked phagocytic properties for lymphoid cells, but not for bacilli. These cells are formed from the endothelium in various places, but principally from the lining cells of the lymph sinuses and from the endothelium of the blood sinuses of the spleen. There is probably also some increase in the

number of lymphoid cells, but relative to the endothelial cells they are few in number. There is but little association of polynuclear leucocytes with the lesions, there is no leucocytosis, the bacilli have no positive chemotaxis for polynuclear cells and these only appear in the lesions in association with necrosis. In the lesions it seems as though the organisms are only accidentally present; they produce no necrosis and the lesions are not more marked in their immediate vicinity. While this is the characteristic action of the typhoid bacilli, foci of suppuration, particularly in the periosteum, may appear during the latter weeks of the disease, or even months after convalescence. Subcutaneous abscesses and abscesses deeply seated in the muscles have been described. Meningitis may be produced by the bacilli and occurs late in the disease or during convalescence. The bacilli find their way into the gall bladder from the blood; they are found there early in the disease and may remain for months and years after recovery. The bacilli also may appear in the urine during the course of the disease, entering this from small lesions in the kidneys. They always are present in the rose spots of the skin. These are small, flat, slightly elevated maculo-papules surrounded by an area of hyperæmia. Histologically there is swelling and oedema of the papillæ and a slight increase in the tissue cells.

#### A CASE OF TYPHOID FEVER

Anatomical Diagnoses. Typhoid fever in stage of beginning necrosis and ulceration; Acute swelling of spleen; Acute degeneration of heart, liver and kidneys; Pressure decubitus of pharynx; Oedema of lungs.

Female, white, age twenty years. Death occurred on the tenth day of the disease. Autopsy ten hours post mortem.

Body of medium size, well nourished. No rigor mortis. Post-mortem lividity marked. Abdomen prominent. Subcutaneous fat in moderate amount, muscles pale. Peritoneum smooth, free from adhesions, the spleen large, dark red, the small intestines distended. Diaphragm right side, fourth interspace; left, fourth rib.

Right pleural cavity free from adhesions. A few long fibrous adhesions over upper lobe of left lung. Pleuræ otherwise smooth, moist and glistening.

Pericardium normal. Heart weight 260 grams. Valves normal. Myocardium lax and pale. Coronary arteries normal.

Both lungs present the same character. There is but little pigment; they are pale anteriorly, the posterior and inferior portions congested, heavy and oedematous. On section of these parts an abundant fluid mixed with air can be expressed. No part sinks in water.

Gastro-intestinal canal. Stomach contains a small amount of fluid mixed with food residue. Mucous membrane rather pale. Duodenum and upper jejunum are normal. Commencing at ileum all of the lymphatic apparatus of the intestine is swollen. The changes are more marked as the cæcum is approached. Commencing at the ileo-cæcal valve and involving the edge of the valve is a large swollen area 10 cm. long and involving almost the circumference of the bowel. The surface of this area is irregular, with elevations and depressions, the color gray. In various places on the surface are opaque gray-yellow areas from 0.5 to 1.5 cm. in diameter and with sharp edges. On section the swollen area varies from 3 to 5 mm. in thickness. The differentiation of the sub-mucous and muscular coats is obscure and the gray swelling extends into the muscularis. On scraping the section with a knife, a thick opaque fluid is obtained; on compression the swelling breaks down into a soft mass.

Peritoneum over the area is smooth. Extending from this upwards a similar change is found in all the Peyer's patches and solitary follicles. The edges of the swollen areas are sharp and spring from the surface without intermediate grades. On several of the Peyer's patches the same yellow, opaque patches on the surface are seen and in one, near the large swelling described, the entire surface is of this character. The swellings corresponding to the solitary follicles are from 2 to 5 mm. in diameter and in places are confluent. In several of them there are small central depressions. The bowel contains a small amount of yellow, thin, fecal material. The appendix shows much the same condition as the ileum. It is swollen, somewhat congested, and on opening it there is a large gray-pink swelling of the mucous membrane extending over the entire proximal end for a distance of 2.5 cm. Beyond this there are larger and smaller swollen areas. The ascending and the transverse colon are thickly strewn with small circumscribed elevations of the same general character as those in the ileum, which correspond with the solitary follicles. They are less numerous in the descending colon.

All the mesenteric lymph nodes and those in the mesocolon are swollen, the single nodes often confluent. In the mesentery 4 cm. from the valve is a large node 4 by 2.5 by 2 cm. in size. All these nodes have about the same character. On section they are homogeneous, rather opaque, of a

gray color, soft, some of them almost diffuent. The post-mesenteric nodes also enlarged, but not to the same extent.

Spleen large, weight 630 grams, the anteroposterior diameter, particularly, increased. Surface smooth, the capsule tense. On section, of a homogeneous rather dark red color, neither trabeculae nor follicles visible, the interior bulges at the section. Consistency soft, an abundant red pulp obtained on scraping.

Liver, weight 1760 grams. The capsule smooth, the surface rather pale, more opaque. Both on surface and on section the lobular markings are obscure, blood contents not increased. The gall bladder of normal size, contains a small amount of dark fluid bile, the wall smooth.

Pancreas and adrenal glands normal.

The kidneys, weight together 305 grams. Capsule easily stripped, surface smooth, rather pale and opaque. On section cortex well differentiated from pyramids, 6 by 8 mm. in thickness, cortical markings obscure, glomeruli not visible. Bladder contains about 500 c.c. of clear urine.

Vagina, uterus and ovaries normal.

Mucous membrane of mouth normal. The surface of tongue dry and brown. The tonsils slightly enlarged. On the posterior pharynx wall corresponding to the position of the cricoid cartilage of larynx is a small transversely situated erosion of the mucous membrane  $\frac{1}{2}$  by  $1\frac{1}{2}$  cm. in size. Larynx and trachea normal. Thyroid normal. Section of femur shows an increase in red marrow and in this there are circumscribed paler foci.

Cultures from the spleen, lymph nodes, liver, bile and blood gave an abundant growth of bacillus typhosus in pure culture.

Microscopical examination. Section through one of the swollen Peyer's patches shows on the surface the epithelial layer in places absent and replaced by necrotic tissue which extends a varying distance into tissue beneath. At the border of the necrosis there is a line of leucocytic infiltration. In the general mass of the swelling the relations of the lymphoid tissue cannot be made out. There are areas and a general infiltration with lymphoid cells, but the mass of swollen tissue is composed of large cells with definite outline, having a thin non-granular cytoplasm, a vesicular oval or curved nucleus containing but little chromatin. These cells contain numerous lymphoid cells enclosed in vacuoles. The enclosed cells are variously altered, the nuclei converted into homogeneous chromatin masses or only chromatin fragments remaining. Some of the large cells contain as many as ten lymphoid cells. The large cells seem to be massed in areas corresponding with lymphatics or lymph sinuses. A small amount of fibrin is contained between the

cells. The blood vessels are not generally apparent. The condition extends throughout the submucosa and along the vascular tracts through the circular muscle coat and to a slighter extent through the longitudinal coat and beneath the peritoneum. The lymph nodes show about the same condition.

The spleen is hyperæmic and shows areas of hæmorrhage. There are everywhere both within the sinuses and without, large endothelial cells of the same character as those in the intestine, but larger and containing great numbers of red blood corpuscles which show various stages of disintegration. In many of the cells there are masses of yellow pigment granules. The follicles are not increased in size and about them and in their interior are large endothelial cells in active phagocytosis.

The liver cells are slightly swollen and granular. In the capillaries everywhere are the large phagocytic cells. In addition to this general distribution there are foci which are composed of these cells, often with strands of fibrin between them. Within some of these foci necrotic liver cells can be distinguished; others are composed of the endothelial cells alone.

Sections of the heart after staining with Scharlach R. show a diffuse formation of very fine fat granules within the fibres.

Sections of the kidney show swelling, vacuolation and irregular granulation of the cells of the convoluted tubules. The glomeruli are normal. Granular masses are found in the lumina and casts in the Henle and collecting tubules.

**REMARKS.** This is a typical case of typhoid, in which the most striking lesion is the infiltration with endothelial phagocytic cells. We must assume that their proliferation is in some way brought about by the bacilli. It may be due to the action of a possible endotoxin stimulating the cells, or some substance arising from the combined action of the bacilli and tissue cells. Usually we can see or fancy we see some purpose connected with the tissue changes, but in this case no such purpose is apparent. The very marked phagocytosis for the lymphoid cells might be thought an attempt to restore the cell balance broken by an increased formation of lymphoid cells, but there is no evidence of this, and in the spleen they devour as actively the red blood corpuscles.

A CASE OF TYPHOID FEVER WITH PERFORATION AND ACUTE  
PERITONITIS

(Only those portions of the autopsy protocol which refer to the lesions are used)

**Anatomical Diagnoses.** Typhoid fever; Ulceration of ileum with perforation; Ulceration of colon; Acute peritonitis; Acute splenic tumor; Acute conjunctivitis.

White male, age forty-two years. Autopsy eighteen hours post mortem. Body well developed and fairly well nourished. Rigor mortis is present. There is lividity of the dependent parts. Pupils are unequal; right 4 mm., left 8 mm. There is no oedema. The right conjunctiva is considerably injected and there is a thin, yellowish fluid in the conjunctival sac. Abdomen is considerably distended.

Peritoneal cavity. On opening this, there is a considerable escape of gas and the wall collapses. It contains 200 c.c. of thin, cloudy fluid, containing fibrin. The blood vessels of the omentum, mesentery and intestines are deeply injected. The transverse and descending colon are markedly distended with gas. There is acute inflammation of the peritoneum, most marked over the lower metre of the small intestine. The appendix measures 7 cm. in length, has a mesentery to tip and no adhesions. Its mucosa is normal. The mesenteric lymph nodes are considerably increased in size, rather soft in consistence, and on section are dark red in color. Diaphragm normal in position.

Spleen. Weight 240 grams. The surface is smooth. Capsule is rather tense. On section the pulp bulges somewhat beyond the capsule. A large amount of blood escapes. The pulp is quite soft and semi-diffuent. The general color is dark red. Malpighian bodies are not apparent.

Gastro-intestinal tract. The peritoneal covering shows acute inflammation. Throughout the lower metre of the small intestine, situated opposite the mesenteric attachment, are several sharply outlined, dark red areas, visible through the peritoneum. Some are almost black. Their general direction is with the long axis of the intestine. Four centimeters from the cæcum there is a perforation through the intestinal wall; the edges of this opening are thickened, everted and covered with fibrin. About the opening the tissue is deeply injected. The perforation is opposite the mesentery in the central portion of an oblong, dark red area. On opening the intestine this perforation is in the centre of a deep ulcer. There are twenty ulcers in the lower metre of the small



intestine. They vary in size, shape and depth. The largest is 2.5 by 2 cm.; the smallest 8 mm. The larger ulcers are deep and shaggy; some involve all of the intestinal wall, their base being formed by the peritoneum. The smaller ones are not so deep. Generally all have elevated and thickened edges and are covered with a purulent exudate. In the cæcum and upper 20 cm. of the colon are several ulcers, generally round to oval, of the same general character as those in the ileum, although smaller. On the posterior portion of the ascending colon, 8 cm. from the tip of the cæcum is an irregularly shaped, ulcerated area 10 by 8 mm. It is quite sharply outlined. The base of this ulcerated area is made up of external muscular coat of the intestine.

**REMARKS.** The condition is self-explanatory. The term "acute splenic tumor" refers merely to the acute swelling of the spleen, which is so characteristic a feature of the disease.

## BACILLUS DYSENTERIÆ

This is a short rod very similar morphologically to the typhoid and to the colon bacillus. It produces no spores, is easily cultivated, and does not stain by the Gram method. Study of the organism has shown that there are several species or strains all of which exert similar pathogenic action. In rabbits the intravenous injection of the organism causes a violent diarrhoea with acute inflammation of the colon. Infection in man probably takes place in the alimentary canal. The lesions produced in man by the organism are in the large intestine and they vary greatly in extent and character. The essential process is inflammation of the mucous membrane usually leading to destruction and ulceration. In certain cases there is superficial necrosis with the formation of fibrinous exudation on the surface which may be extensive or occur in small foci (diphtheritic dysentery). The exudation is most marked on the surface of the folds of mucous membrane. The ulcers may be single and small, or numerous and extensive. In the acute summer dysentery of young children, the intestinal lesions may be limited to a few small ulcers. In both the acute and chronic forms the mucous membrane may be destroyed over large areas, leaving elevated islands of intact surface. There is nothing characteristic in the appearance of the ulcers. Dysentery as produced by this organism may appear sporadically or in epidemic form.

### A CASE OF ACUTE EPIDEMIC DYSENTERY WITH CHRONIC MALARIA

This case was one of a number of cases which occurred during an epidemic of dysentery in a large asylum. The disease was very fatal, the mortality reaching 35 per cent. The population of the asylum consisted largely of debilitated anæmic old people in whom the greatest mortality occurred.

Anatomical Diagnoses. Acute epidemic dysentery; Necrosis and ulceration of colon and rectum; Chronic malaria; Anæmia; Necrosis of liver; Hyperplasia of lymph nodes; Œdema of lungs.

White male, age sixteen years. The body of ordinary size, emaciated, the surface pale with slight icteric tint. Subcutaneous fat small in amount; the muscles pale.

Peritoneum smooth. About 200 c.c. of clear fluid with slight yellow tint in the cavity. The peritoneal surface of the colon injected. All the lymph nodes in the meso-colon enlarged and pale red in color. The mesenteric and post-peritoneal nodes slightly enlarged.

Pericardium normal. In the cavity a few cubic centimeters of clear, slightly yellow fluid.

Heart weight 270 grams. Myocardium pale and friable. Endocardium and valves normal. The pleuræ free from adhesions, the fluid in cavity slightly increased in amount.

The lungs. The surface pale with carbon tracings along the pleural lymphatics. On section considerable fluid mixed with air exudes from the posterior portions of each lung. The mucous membrane of bronchi pale.

Liver weight 1450 grams. The organ a pale slate color. The surface smooth. On section, consistency normal, the lobules visible.

The spleen. Large, weight 235 grams. The surface smooth, the organ of a deep slate color, consistency firm, follicles prominent against the dark background. On scraping, the pigmented pulp comes away.

The pancreas normal.

Intestinal canal. Mucous membrane of stomach and upper part of small intestine pale. The follicles and Peyer's patches prominent. For a space of 20 cm. above the ileocæcal valve the mucous membrane of ileum is swollen, deeply injected, and over the surface there are pale, opaque and rather dry flecks which tend to occur in lines transverse to the axis of the gut. In places there are small foci of hæmorrhage. This condition is not more marked over the Peyer's patches than elsewhere. There is no ulceration save on the surface of the valve where there are a few superficial irregular losses of substance. The mucous membrane of the ascending and the beginning of the transverse colon is swollen and hyperæmic. On the surface there are a few scattered pale, opaque flecks similar to those described in the ileum. Commencing in the middle of the transverse colon the swelling and hyperæmia of the mucous membrane is more intense, and the spots of exudation on the surface more numerous, these coalescing in places to form a dry gray, opaque membrane which is firmly adherent. On section this condition in places involves the entire thickness of the mucous membrane; in places it is superficial. It is more marked on the surfaces of elevations than elsewhere. The scattered flecks are so sharply circumscribed as to present an appearance as though some foreign material had been scattered over

the surface. In the lower portion of the descending colon and in the upper rectum the condition gives place to extensive ulceration. The ulcers in places are so extensive that but irregular islands of mucous membrane appear on the surface. The ulcers are superficial not passing into the muscularis. They are smooth on the surface, not necrotic, and the base is red and granular. The smaller ulcers show no undermining; the edges are sharp and of irregular shape. The ulceration extends to 6 cm. above the anus.

Kidneys, combined weight, 270 grams. Capsule not adherent, the surface smooth rather pale. On section pale, opaque; the markings of cortex accentuated; the pyramids pale.

Ureters, bladder and urethra normal.

Neck organs. The mucous membrane of mouth and pharynx pale; the tonsils slightly enlarged. The mucous membrane of larynx and œsophagus pale.

Meninges and brain present no lesions.

Microscopic examination. A marked degree of fatty degeneration in myocardium both diffuse and focal. It is most marked in the inter-ventricular septum and at the bases of the papillary muscles of left ventricle.

The liver contains much fat in the cells in the form of small droplets irregularly distributed. Almost everywhere there are areas of necrosis around the central veins of the lobules which vary in size, in some of the larger extending to the middle of the lobule. In most places and particularly in the larger areas the necrotic cells are invaded by polynuclear leucocytes. In the sinuses there are numbers of large endothelial cells containing black pigment in round or irregular variously sized granules. In places the pigment is contained in cells of the same character but which are attached to the walls.

The spleen shows large masses of pigment which in part is within large cells similar to those in the liver; in part appear to be free. The follicles are enlarged and in the centres of many of these there is much nuclear detritus and among this large pale ovoid nuclei. Here and there the cytoplasm belonging to these nuclei can be distinguished, and contains much of the free nuclear detritus.

Sections through the colon involving the scattered flecks on surface show circumscribed necrosis of mucous membrane, most extensive on the surface. There is much hæmorrhage in connection with this and fibrinous exudation, the necrosis hæmorrhage and exudation combining to form lenticular patches which extend above the surface. In the splenic flexure the necrosis and exudation are more extensive involving the entire mucous membrane but in no place extending into the sub-

mucosa. In this the blood vessels are injected and contain numerous leucocytes. In places there are slight hæmorrhages and a small amount of fibrinous exudation in the form of thin fibrin filaments. There is a general infiltration of cells, in large part small lymphocytes, more marked around the veins. There are also a number of endothelial and plasma cells. In the ulcerated areas the bases of the ulcers extend in places to the muscularis but usually they are more superficial.

REMARKS. This is a typical case of acute epidemic dysentery caused by the bacillus dysenteriae, either the Shiga or Flexna type. The autopsy was made in 1881 before the time when cultures were customary. In the institution at this time it was recognized that there were two anatomical types of dysentery but no etiological differentiation could be made. Compare the lesions in this case with those of amœbic dysentery, page 314. Lesions so extensive as in this case are not usual. In young children there may be focal hyperæmia merely or a few superficial ulcers.

## CHOLERA SPIRILLUM

This is a small slightly curved rod, the curve in the three dimensions of space. It is actively motile, has a single polar flagellum, does not stain with Gram and produces no spores. It grows readily in the ordinary culture media, the temperature limits being 22–40° C. Alimentary canal infection can be produced in animals after neutralization of the gastric juice with sodium carbonate, and the use of opium to prevent active peristalsis. The toxic properties of the organism are due chiefly to endotoxins, the formation of true secretory toxins being uncertain.

Cholera is a human disease, and infection takes place in the alimentary canal. The organisms can be transmitted by contact, by use of infected articles and chiefly by the contamination of water supplies. The organism grows in the alimentary canal and produces an acute inflammation of the surface with destruction and desquamation of the epithelium. The organisms are present in great numbers, but there is no tendency to invasion. The tissues are dry and the blood rendered more viscid owing to the great amount of serous exudation poured into the intestine.

## BACILLUS COLI COMMUNIS

This is a short, plump organism, a constant inhabitant of the alimentary canal of man and of other warm-blooded animals. It grows readily in most culture media at temperatures between 20° and 40°; it is not an exclusive parasite; it is provided with flagella, forms no spores and is decolorized in the Gram stain. It is slightly pathogenic for laboratory animals. The virulence of different strains of the bacillus varies greatly. The toxic action is due to endotoxins.

Secondary and terminal invasions of the body by the organism are common. In almost all lesions of the alimentary canal, however produced, colon bacilli are found in the organs on culture. Pyelonephritis, the acute inflammation of the kidney due to the extension to the kidney of an infectious process lower down in the urinary track, very frequently is produced by the colon bacilli. Cases of cholecystitis and cholangitis and associated abscess of the liver may be due to this organism. It often is associated with other organisms in lesions and it is uncertain in these cases what part it plays in their production.

### A CASE OF INFECTED THROMBUS OF MESENTERIC VEIN WITH ABSCESES IN THE LIVER ASSOCIATED WITH COLON BACILLUS

Anatomical Diagnoses. Appendectomy; Acute peritonitis; Purulent pylephlebitis with thrombosis; Emboli in liver with multiple abscess formation; Jaundice; Acute hyperplasia of spleen; Acute degeneration of kidneys.

White, male, aged fifty-two years. Two years previous to present illness had severe pain in right lower quadrant of abdomen. Present sickness began with pain in same region which rapidly increased in intensity and was accompanied by vomiting and chills. Blood count showed a leucocytosis of 29,200. Tenderness over right iliac region. At operation the appendix was found swollen, dark colored and hard. On tying the ligature around it previous to excision, it was torn across

and a small amount of the contents escaped soiling the edges of the wound. On the third day after operation marked jaundice developed with chills and high fever followed by profuse sweating. A blood count made at this time showed a drop in the leucocytosis to 15,000. The rectal temperature varied between 102 and 106 degrees. Death on the fourth day after operation. Incision at autopsy limited to abdomen.

Body well developed and well nourished. The abdomen distended. Rigor mortis of legs. Skin everywhere of a bright yellowish color. Conjunctivæ greenish yellow. In the abdominal wall in the region of the right rectus muscle is an oval wound opening into the abdominal cavity. Subcutaneous fat in fair amount and greenish yellow in color.

The omentum is firmly adherent to the edges of wound and to the underlying loops of the intestine. The right iliac fossa contains 10 c.c. of thick, creamy pus streaked with blood. The spleen large and adherent by soft fibrinous adhesions. The general peritoneal surface is cloudy, with a few flocculi of fibrin over intestines. The small intestines distended with gas.

The gall bladder is distended, its ducts free. The portal vein and its gastric and splenic branches free from clots. The superior mesenteric vein beginning at its extremity near the appendix is filled with a firmly adherent gray-red thrombus. The wall of the vein is distinctly thickened and soft. The clot in places is soft and purulent, and near to the opening into the portal vein the lumen of the vein contains a thick purulent material.

Beginning at the entrance of the portal vein into the liver all the portal branches contain pus. Throughout the liver extending in the direction of the portal veins are numerous abscess cavities, their walls irregular, due to the union of contiguous abscesses. The cavities are surrounded by areas of necrotic liver tissue. They contain a thick greenish yellow pus. Some of the abscesses are near the surface and separated from the peritoneal cavity by the capsule of the liver only.

Spleen, weight, 340 grms. Fibrinous adhesions chiefly over posterior surface. On section soft, edges of incision bulging, dark red in color. Follicles not prominent.

Pancreas normal.

Kidneys weigh 315 grams. Capsules nonadherent. Cortex of bright yellowish red color. Markings normal.

Cultures from liver abscesses show colon bacilli in pure culture.

Sections of the liver show abscesses with extensive necrosis, purulent infiltration and softening in surrounding tissue. In places branches of the portal vein are found filled with granular material containing masses of bacteria, the walls necrotic and surrounded by necrotic liver tissue.



The portal tissue in the intact areas of the liver is infiltrated with lymphoid cells.

The spleen shows intense hyperæmia with foci of hæmorrhage. The malpighian bodies are not enlarged.

In the kidneys there is cloudy swelling, fatty degeneration, with here and there necrosis and desquamation of the cells of the convoluted tubules. The necrotic cells contain bile pigment, and deeply pigmented hyalin casts are found chiefly in the collecting tubules.

**REMARKS.** A recurrent attack of appendicitis of a severe character terminating in gangrene of the appendix. The blood count shows an acute inflammatory leucocytosis, and the fall in the number of leucocytes after the operation is of importance in showing a lack of resistance. The acute peritonitis is the result of peritoneal infection which may have taken place at the time of operation or preceding this. The acute phlebitis with thrombus formation is the result either of infection of the vein from the peritoneal focus or there may have been infection of a small branch leading from the appendix. In either case there was extension in the continuity of the vein. The thrombi, so formed, underwent purulent softening and gave rise to numerous infectious emboli which were carried to the liver and produced the abscesses. The jaundice results from occlusion of the bile ducts by the abscesses. The acute swelling of the spleen is the consequence of congestion due to the occlusion of the hepatic branches of the portal vein, and the acute degeneration of the kidneys, which is a constant feature in acute jaundice, is due to the action of the bile salts on the epithelium.

## ENTAMŒBA HISTOLYTICA

Amœbic dysentery is a form of chronic inflammation of the large intestine with ulceration caused by the entamœba histolytica. This organism is from 15 to 25  $\mu$  in diameter. It consists of a clear hyalin outside area, the ectosarc, surrounding a granular area, the entosarc, which contains the nucleus. The organism when obtained from fresh stools, and particularly on the warm stage, is actively amœboid, large blunt processes of the ectosarc being thrust out into which the granular entosarc flows. The amœbæ are phagocytic and red blood corpuscles, other cells and bacteria often are within them. The nucleus is single, large and vesicular consisting of a nuclear membrane from the internal surface of which bits of chromatin project. In sections of the intestine the amœbæ can be recognized by an outer membrane, seemingly formed by the contraction of the ectosarc, and an interior shrunken mass of granular cytoplasm. The intestinal lesions consist of ulcers which are greatly undermined and often connected by sinuous passages in the submucosa. The submucosa in the vicinity of the ulcers is swollen by an cedamatus and fibrinous exudate. The amœbæ are usually most abundant where the undermining of the mucous membrane is advancing. The leucocyte reaction is slight; the cellular infiltration in the submucosa consists of lymphoid and endothelial cells. The term "histolytica" describes well the action of the amœbæ in producing histolysis of the tissue about them. The intestinal lesions are almost characteristic but in rare instances ulcers of a similar type may be found in chronic bacterial infection of the intestine. In connection with the intestinal lesions, abscess of the liver, due to the embolic extension of the amœbæ into the liver, not infrequently are found. Abscess of the liver may also be produced by the amœbæ extending directly into the liver from the hepatic flexure of the colon which has previously become adherent. The same process of gradual liquefaction of tissue takes place in the production of the liver abscess, as in the extension of the ulceration in the submucosa of the

intestine. Similar conditions may be caused by the *entamoeba tetragena* but the *entamoebacoli* is a nonpathogenic inhabitant of the colon.

#### A CASE OF AMOEBIC DYSENTERY WITH LIVER ABSCESES

**Anatomical Diagnoses.** Multiple amoebic abscesses of liver; Circumscribed amoebic peritonitis from perforation of liver abscess; Operation wound into abscess of liver; General fibrino-purulent peritonitis; Amoebic dysentery with perforation; Emphysema of lung; Anthracosis of lung.

The body that of a man about fifty years old, rather small, slightly built, greatly emaciated. Body length 171 cm.

In the anterior abdominal wall, in the median line, commencing close beneath the ensiform cartilage, and extending downward a little to the right side, is an incision 6 cm. long, closed by fine sutures. Subcutaneous fat slight in amount. Muscles dark; abdomen retracted.

Heart, weight, 340 grams. The pericardium in one place firmly adherent. The myocardium rather dark. Valves normal. Coronary arteries normal.

Aorta normal.

Both lungs free from adhesions, save along diaphragm, where there are slight, easily broken-down fibrinous adhesions. Both lungs in high degree emphysematous; very dark in color from coal pigment. Bronchi slightly dilated, pale; otherwise normal.

Before opening abdomen slight induration could be felt in left hypochondrium. On opening abdomen the incision in abdominal wall is found to pass into a sac on the lower border of the liver. The transverse colon is adherent to the anterior abdominal wall, shutting off the peritoneal cavity below. The small intestines are slightly adherent to one another, and in places between the folds, and especially toward the root of the mesentery, there are masses of gelatinous looking fibrin. The same gelatinous looking fibrin extends down into the pelvis. There is an abscess cavity which extends along the left border of the liver, between that, the colon, the stomach, the spleen and the abdominal wall. This abscess cavity is filled with a gray, more or less tenacious, fibrinous, gelatinous pus. Along the hepatic side of the transverse colon there is an abscess communicating with the first abscess by a small opening, and which is filled with a yellowish purulent material. There are several large openings from the transverse colon into this abscess. All of the tissues bordering upon the abscess appear to be more or less softened as though from the action of gastric juice.

The liver is not enlarged. On the anterior lower border of the liver there is a large sac which extends directly into the liver, and which is continuous with the peritoneal abscess. This sac is filled with a thin yellowish material. Its walls are deeply stained with bile. On section of the wall there is everywhere a hard, fibrous limiting membrane. In a few places there are pockets filled with the gelatinous pus described before, which extend from the abscess wall into the liver. This abscess cavity measures 8 by 6 cm.

On cutting into the liver in the middle of the right lobe there is an abscess cavity 4 by 3 cm. in diameter. This presents on section a granular reticular-looking mass, yellow and necrotic, and in the meshes of the reticulum there is thick, gelatinous looking pus. This abscess cavity is not very sharply circumscribed, but the necrotic tissue extends directly into the liver. On the upper surface of the liver, between that and the diaphragm, there are fresh, easily broken-down adhesions, composed of gelatinous fibrin. The bile ducts are dilated.

The spleen, weight, 135 grams. Dark; its capsule wrinkled and covered with a gelatinous, fibrinous, purulent mass. The spleen forms part of the abscess cavity first described.

The mucous membrane of stomach somewhat hyperæmic, otherwise normal. The duodenum normal.

The large intestine throughout contains numerous ulcers. Beginning at the cæcum, in the ascending colon the mucous membrane is swollen, thickened, gelatinous, and here and there in it there are small circular undermined ulcers, the largest of them 1.5 cm. in diameter, with gelatinous purulent infiltration of the submucosa extending for some distance around the ulcer. In the transverse colon the lumen is dilated, the mucous membrane is thickened, and everywhere there are large ragged ulcers covered with gangrenous black sloughs; the surrounding mucous membrane, where it is preserved, is thickened; the submucosa infiltrated. The intestine contains a yellow, rather thick, more or less viscid, material. Several deeper ulcers have perforated into the peritoneum.

Kidneys. Combined weight 360 grams. Capsule strips easily. Cortex and pyramids normal. Markings somewhat obscure.

Adrenal glands and pancreas normal.

Pelvic contents normal, with the exception of rectum, in which similar ulcers to those in the ascending and descending colon are found.

The microscopic examination of the contents of the abscess of the liver and of the intestine shows large numbers of vacuolated amœbæ, in some instances containing red blood corpuscles. Movement could be made out in but few of these. Amœbæ also were found in the gelatinous material in the general peritoneal cavity.

**REMARKS.** This autopsy with the exception of the peritoneal abscess is fairly typical of amoebic dysentery. The character of the lesions in the colon and the character of the liver abscesses is indicative of amoebic infection. The pus in the liver abscesses usually contains the gelatinous viscid material described here. In the absence of continuity with the intestine from perforation they usually contain no bacteria. The main interest in the case apart from the amoebic infection is in the peritoneal abscess. In this region of the peritoneal cavity, peritonitis from infection tends to become circumscribed by the formation of adhesions and the exudate lies in a cavity resembling a pus cavity. The infection in this region is usually due to perforation of the stomach by ulcer or by cancer, or it may be due to extension of infectious process from the gall bladder, or, as in this case, to perforation of the colon. The disease is really within the thoracic cavity and since gas from the intestine is usually contained in the space the condition is known as "subdiaphragmatic pyo-pneumo-thorax."

## PLASMODIUM MALARIÆ

Malaria is produced by a blood parasite, one of the hæmosporidia which is parasitic in the red blood corpuscles of man. The parasite undergoes a definite cycle of development, the sexual phases of which take place within mosquitoes. The disease is characterized by periods of chill followed by high fever which in certain forms of the disease occur with definite periodicity, in other forms are of a more irregular type. According to the clinical course of the disease, it has been divided into different forms, each of which is produced by a different species of the parasite.

The forms of the disease are the tertian, in which the paroxysms occur with one free day in between, and which is produced by the plasmodium vivax; the quartan, in which the period of fever is followed by two days of freedom from attack and which is produced by the plasmodium malarix; the æstivo-autumnal, in which the fever is of a more irregular type. In certain cases the æstivo-autumnal fever is continuous, closely resembling typhoid; in other cases slight attacks of fever occur daily; and in others the fever takes a pernicious form, the patient dying in coma during an attack. This type of malaria is produced by the plasmodium precox or falciparum.

When the blood is examined shortly after the period of chill there will be found within or on the surface of certain of the red blood corpuscles small ameboid bodies about one-fourth the diameter of the corpuscle. The organism increases in size, successively attacking and destroying red blood corpuscles. These lose their hæmoglobin, become greatly swollen and break up. With the increase in size of the organism dark granules of pigment begin to appear, at first irregularly distributed within the body, later collecting in the middle. The organism then divides into a number of segments which again attack new corpuscles and pass through the same cycle. All the organisms show the same stages of development at the same period, and the segmentation corresponds with the period of chill. In the quartan fever the same stages, which in the tertian have taken forty-eight hours, take seventy-two. In the æstivo-autumnal fever

the plasmodium precox has a cycle of development of forty-eight hours, but this probably is subject to considerable variation, while the existence of multiple groups is not infrequent. This asexual multiplication of the parasite is known as schizogamy and the young parasites as merozoites. The merozoites, when taken into the alimentary canal of the mosquito of the genus anopheles, undergo a further development into male and female forms known respectively as micro- and macro-gametes, and after fertilization a large body, the oökinet which attaches itself to the intestinal wall is formed. Small sickle-shaped bodies, the sporozoites, which pass into the body cavity of the mosquito and make their way into the salivary glands develop from the oökinet. When the insect bites man, it injects a small amount of saliva, which in the case of infected mosquitoes, carries with it the sporozoites. These quickly reach the blood and institute the asexual cycle of multiplication.

The lesions in malaria are due to the destruction of blood corpuscles by means of the parasites and to toxic substances which apparently are set free when the organism divides, thus producing the chill. There are also lesions associated with the presence of the pigment and lesions due to the plugging up of the capillaries in certain regions of the body, particularly in the brain, by the numbers of organisms within them. During the attack the spleen is enlarged and soft. When the disease has persisted, the spleen remains enlarged and is dark or often black from the amount of pigment within it. There is a marked increase in the interstitial tissue of the spleen causing induration. The liver also is somewhat swollen and within the sinusoids are great numbers of large phagocytic cells which contain pigment. This pigment, which is such a characteristic feature of the disease, is autochthonous, is produced by the parasite and does not contain iron. The æstivo-autumnal fever in certain regions has a peculiarly malignant type, death taking place in the period of chill. The malignant course is to be attributed either to the presence of great numbers of organisms, or to their especial virulence, or to lack of resistance in the individual. In death from this condition the brain is of a chocolate brown color, which is due to enormous numbers of the parasites often in the stage of segmentation within the capillaries of the gray matter. Large numbers of organisms may also be found in these conditions in the spleen and in other organs.

## A CASE OF PERNICIOUS MALARIAL FEVER

The patient was received into the hospital in the afternoon of September 12th, 1884, in a profoundly comatose condition, with a temperature in the axilla of 101.4° F. Sickness began two days before with complaint of loss of appetite and general weakness. He became unconscious in the morning of the day he was sent to the hospital. He died on September 13th at 9 A.M. without having regained consciousness.

(Only the lesions associated with the disease are noted.)

The pia mater slightly thickened and œdematous, easily stripped from the surface of the brain. The cortex of the brain throughout is of a dull chocolate color, this color more pronounced in the gray than in the white matter, although the white matter is slightly darker than normal, and the line of demarkation separating white from gray is more pronounced, giving the gray matter the appearance of being lessened in width. The central ganglia of the brain are of the same dark color as the cortex. The pia arachnoid of the cord is hyperemic, the cord itself darker, the gray matter of the same color as the cerebral cortex.

Liver large, weight 2126 grams. Of a dark slaty color, very hyperæmic.

Spleen greatly enlarged, 18 by 10 by 5 cm., weight 825 grams; hyperæmic, of a dark, almost black, color.

On microscopic examination of the brain cortex with low power, the blood vessels have the appearance of being artificially injected with a black injecting mass. With a high power the small granules of pigment are found to be, for the most part, within small hyalin masses enclosed in red corpuscles. Often the pigment granules are in the centre of small rosettes formed by segments radiating from a centre. The white matter of the brain also contains the pigmented bodies, but they are less numerous than in the cortex. In the cord the blood vessels are filled with hyalin pigmented masses which are more numerous in the gray than in the white matter. In the spleen there is a large amount of pigment, in part free, in part contained in large endothelial cells, and in part contained in minute masses within the parasites. In the liver the sinusoids contain great numbers of large endothelial phagocytic cells filled with pigment granules of irregular size.

**REMARKS.** The condition is sufficiently explained by the preceding text.



## SMALL POX

This is an acute infectious disease characterized by a pustular eruption on the skin. The skin lesions begin as vesicles which later are converted into pustules. The factors concerned in the production of the vesicles are degeneration of the epithelial cells associated with or followed by an exudation into the epidermis. The degenerated cells form a reticulum within the meshes of which the exudation accumulates. Section of the vesicle shows a fan-shaped reticular structure within the epidermis and a varying number of leucocytes in the spaces. In the corium the blood vessels are congested and there is a slight exudation about them. As the exudation increases the tension becomes great, and strands of the reticulum rupture and large spaces separated by shreds of epithelium are formed. The vesicle becomes converted into a pustule by the accumulation of leucocytes in the exudation. In slight lesions the malpighian layer of epidermis may be intact, but in the more extensive lesions not only is the entire epidermis involved, but there also is necrosis of the papillæ. When the papillæ of the corium are destroyed a smooth depressed cicatrix remains after healing. In most cases the pustules are depressed, in the centre, umbilicated, due to the presence in the centre of more resistant epithelial structures such as ducts of sweat glands or hair follicles. The pustules vary in size from 2 to 8 mm. The severity of the disease usually is in direct proportion to the extent of the eruption. The pustules may be single and few in number, *discrete smallpox*, or so numerous that adjoining vesicles coalesce, *confluent smallpox*. The eruption appears first and the pustules are more numerous on the face. They are more numerous on the extremities than on the trunk. In certain severe forms of the disease the exudation may have a hæmorrhagic character *variola pustulosa hæmorrhagica*. A special form of the disease, *purpura variolosa* (black smallpox), is characterized by intense congestion and hæmorrhage of the skin and a slight development of pustules. The erythema develops quickly after the onset of the disease and death takes place before the pustules develop.

The cause of smallpox remains obscure. In the lesions of the skin, bodies of peculiar character are found in the epithelial cells in a space adjoining the nucleus (*cytocytes variolæ*). They are invariably present and reach the acme of their development before the pustular stage; with the development of the pustule, peculiar vacuolated bodies appear in the nuclei. In vaccinia, which must be regarded as a form of smallpox, the virus of which is modified by passing through the cow, inclusions in the epithelial cells similar to those found in the vesicular stage of smallpox are invariably present. The inclusions within the nuclei of the epithelial cells are not found in vaccinia. These inclusions have been regarded as living organisms related to the protozoa, the reason for this conclusion being based on their invariably presence in the disease in association with the lesions and under no other conditions, the evidence of growth and development which they show and the dissimilarity with other products formed in cells as the result of degeneration. The positive proof for this conception of their nature, which could be given by isolation and culture, is absent.

Lesions in their main characteristics similar to those of the skin are found in the mucous membrane of the mouth and pharynx. Typical vesicles and pustules do not form, owing to the absence of the impenetrable horny layer. In addition to these lesions of the skin and mucous membranes, lesions equally characteristic, but not so constant, occur in the testicles and in the bone marrow. In the testicles the lesions take the form of small foci of necrosis of the tubules, with hæmorrhage and fibrinous exudation in the interstitial tissue and with infiltration of cells of the lymphoid type. They appear as small red foci rarely more than 2 mm. in diameter. The lesions in the marrow consist in degeneration, focal in character, apparently not anæmic, but due to toxic action, leading to necrosis often associated with hæmorrhage, and accompanied by focal formation of phagocytic cells.

Diffuse toxic degeneration is present in the liver, the kidneys, the adrenal glands and the testicles; in the liver cloudy swelling is more marked than it is in any other infectious disease and gives rise to a considerable increase in the weight of the organ.

Secondary bacterial infections, particularly with streptococci, play an important rôle in the pathology of the disease and in most cases death is to be attributed to such secondary infection. The

infection with bacteria often extends from the specific lesions of the mucous membrane of the mouth or pharynx into the adjoining tissue, producing extensive necrosis and oedema. Bacteria in large masses may be found in the tissue growing as in culture and without any leucocytic reaction about them. Broncho-pneumonia also is common and may be extensive.

Smallpox is transmitted through the placenta and children are born with characteristic skin lesions, and in some cases with the cicatrices which follow them, having passed through the disease in utero.

#### A CASE OF SMALLPOX

**Anatomical Diagnoses.** Variola confluens, crusting on face, pustular and vesicular elsewhere; Oedema of lungs; Focal necrosis of the testes; Focal lesions of the pharynx, trachea, oesophagus, and urethra; Acute laryngitis, tracheitis and bronchitis; Plegmonous inflammation of neck and anterior mediastinum.

**Clinical Diagnosis.** Variola vera (twelve days' duration.)

Body of a well-developed and well-nourished man, thirty-six years of age. Rigor mortis present and fully developed.

The face and neck present a confluent mass of soft, moist, brown crusts. The nostrils are almost occluded by crusts. Left eye is absent (old injury). Right eye and conjunctiva normal, pupil of normal size. Over the trunk there are numerous late vesicles and early pustules. The lesions are four to eight millimeters in diameter, are of the color of the skin, show a marked umbilication, and sometimes have a slightly oval outline. These lesions are not very closely set (about one to a centimeter square.)

On the arms and legs are many lesions like those on the body, but they are more closely set and somewhat larger, particularly on the dorsum of the hands. On the penis and scrotum are a considerable number of similar lesions.

On the thighs are closely set, umbilicated vesicles, like those described on the body. The lesions here are about two or three to the square centimeter. On the legs and dorsa of the feet the lesions are fewer in number and are less umbilicated. There is no clustering of the lesions and in the groins and flanks they are comparatively few in number. There is a purulent balanitis.

On section, subcutaneous fat 3 cm. thick. Muscles deep red. Mesenteric lymph nodes and appendix normal.

**Thorax.** Pleural cavities; surfaces normal. Pericardial cavity normal, contains a few c.c. of clear, straw-colored fluid.

**Heart.** Weight 260 grams. Myocardium pale brown red. Right ventricle flabby and filled with yellow clot. Left ventricle firmly contracted. Valves and cavities normal.

**Lungs.** On the outer aspect of the left lower lobe is an area of thickened pleura 1.5 cm. across, which is of a pearly-white color and with a serrated border. Lungs alike. Crepitant throughout. On section, cut surface mottled light and deep pink with distinct carbon markings. Surface, on gentle pressure, yields considerable clear fluid containing innumerable bubbles of air. Bronchial mucosa normal. Bronchi contain stringy mucus.

**Abdomen.** Peritoneal cavity normal.

**Spleen.** Weight 200 grams. Color, deep purple. On section cut surface deep red, malpighian bodies visible as gray points; trabeculae normal. Consistency is firm, and little substance adheres to knife on gentle scraping.

**Pancreas** normal.

**Stomach.** Some diffuse ecchymoses along lesser curvature. Mucosa normal.

**Intestines;** normal.

**Liver.** Weight 2650 grams. Surface smooth and of a yellow-brown color. On section, markings indistinct. Consistency normal. On the surface are irregular yellow areas which are contoured in such wise as to suggest aggregations of fatty lobules. On section similar markings are found. Gall bladder normal.

**Kidneys.** Weight 350 grams. Surface yellow brown. Capsule strips readily, leaving a smooth surface. On section markings are indistinct. Glomeruli visible as gray points. Cortex of normal thickness and of a yellow-brown color. Pyramids reddish brown.

**Adrenals** normal. **Bladder** normal.

**Genitals; urethra.** About midway in the penile portion is an elevated area 2 mm. across, with an irregular, oval outline and with a central depression. Elsewhere urethra is normal. Seminal vesicles and epididymis normal. Prostate normal. Testes; tunica vaginalis normal, slightly nodular to the feel. On section the markings are distinct, but scattered over the cut surface are nodular elevations 1 to 3 mm. across, which are redder than the surrounding tissue. These areas are not sharply circumscribed, and in them the tubular markings are visible.

**Lymph nodes** of the groin are enlarged, red and somewhat hard. (Largest, 2 cm. across.)

**Aorta** normal.

Organs of neck. Soft palate; uvula and pharynx show low, gray nodular elevations, some of which present a central superficial loss of substance.

Epiglottis thickened and similarly beset with nodules.

Larynx contains much gray mucus and its mucous membrane is reddened. In the trachea are numerous elevations from 1 to 3 mm. in diameter, surrounded by a red ring. These elevations are conical and are occasionally eroded. About thirty such lesions of various sizes are present. Oesophagus, upon its mucous membrane, presents many pale gray, oval or circular elevations, from 1 to 3 mm. in diameter. The largest of these is a low cone, of a translucent gray color, surrounded by a narrow elevated rim like the hull of an acorn; this surrounding rim is red.

The deep tissues of the neck on the right side are infiltrated with a grayish material, and on section a considerable amount of turbid, slightly blood-stained fluid exudes. The jugular vein is filled with a yellow clot and its wall appears normal. The muscles close about the larynx are in part friable and of an opaque, yellow-brown color. The fibrillary markings are indistinct. The tissue of the anterior mediastinum is oedematous, and on section a cloudy, faintly blood-stained fluid exudes. This condition is most marked over the precordium and about the remnant of the thymus. Left side of neck normal.

Bone marrow, in general, yellow with many areas of deep red color.

**REMARKS.** The case is one of typical smallpox with death on the twelfth day of the disease. The character and distribution of the eruption on the skin is the usual. The pustule in the urethra is an unusual localization. The extensive infection of the neck which has extended into the mediastinum is due to streptococci which probably have entered the tissue from the tonsil or pharynx. The character of the lesions in the mucous membrane with the generally eroded surface is interesting in contrast to the pustules in the skin.

## MEASLES

This is an acute infectious disease characterized by a maculopapular eruption of the skin and mucous membranes.

An incubation period, usually of fourteen days, is followed by fever, coryza, bronchitis and the appearance on the buccal mucosa of white or bluish-white specks surrounded by a small red areola. (Koplik's spots.) The cutaneous eruption appears first behind the ears, then extends to neck, forehead and face, thence to the trunk and extremities. The eruption consists of small macules of light red color, vaguely defined and often confluent, whose elevation is so slight as to be more readily detected by touch than by the eye.

This disease is made a serious one by the frequent development of broncho-pneumonia. Otitis media frequently is a concomitant and sequel; acute nephropathy is not infrequent.

## SCARLET FEVER

An acute infectious disease characterized by diffuse erythematous eruption. The gross pathological lesions are slight and the erythema usually does not show after death. The only constant gross change is hyperplasia of the lymphoid tissue generally. The blood vessels of the corium are dilated more especially near the epidermis and in the papillæ. The superficial lymphatics and lymph spaces likewise show dilatation in the same situation. With these changes there is a slight exudation. Leucocytes, in small numbers, migrate from the blood vessels and are found in the corium and invading the epidermis. In the tongue there are pathological conditions similar to those in the skin, but they begin earlier and are more marked and the same is true of the mucous membrane of the pharynx and tonsils. Bodies which have been interpreted by some as products of cell degeneration and by others as protozoa occur in the epidermis in association with the lesions (cyclasterion scarlatinalis). These bodies are found lying in vacuoles in the epithelial cells of the epidermis, to a less extent between these cells, and free in the superficial lymph vessels and spaces of the corium. Associated with these specific changes frequently are found broncho-pneumonia and otitis media which are due not to the specific cause of scarlet fever but to secondary infections usually with the streptococcus. The period of incubation usually is four or five days.

### A CASE OF SCARLET FEVER

Anatomical Diagnoses. Focal hyperæmia of the skin with slight desquamation (scarlet fever); Thrombi in heart; Acute endocarditis of mitral and aortic valves; Acute pericarditis; Acute peritonitis; Acute bronchitis and broncho-pneumonia; Acute interstitial nonsuppurative nephropathy; Fatty degeneration of the heart; Focal necrosis of the liver; Acute otitis media; Streptococcus and pneumococcus infection.

Female, white, age five years. There are irregularly placed areas of hyperæmia of the skin most marked over the neck, posterior part of the body and legs, and over the anterior surface of chest and arms. In these

areas there are small elevated points with slight exfoliation of the epidermis.

The abdomen is slightly distended and the cavity contains a small amount of clear fluid. Over the surface of the liver there is a thin layer of fibrin, and over the peritoneal surface elsewhere a few areas covered with a slight fibrinous exudation.

The pleural surfaces on the right side are adherent by fibrous tissue; on the left free. The pericardial cavity contains a small amount of cloudy fluid. Both the visceral and parietal surfaces are covered with a thin layer of fibrin.

Heart, weight, 100 grams. In the right auricle near the auricular appendix is a small white adherent thrombus, 1 cm. in diameter, and in the appendix a number of small thrombi. Along the line of apposition of the mitral valve there are numerous small gray elevations, the largest 1 mm. in diameter. On one of the cusps of the aortic valve there is a small group of similar granulations. The myocardium is pale, and in one of the papillary muscles there are numerous yellow-white foci.

The lungs are distended. The pleural surface hyperæmic with scattered foci of more marked hyperæmia and which are solid to the touch. On section the lungs are congested and oedematous, and throughout there are small pale red areas of solidification from 0.5 to 1 cm. in diameter and from which a purulent fluid can be expressed. The mucous membrane of the bronchi is reddened and a purulent exudation can be expressed from thin sections in the lung.

Spleen, weight, 105 grams, firm, dark red, follicles prominent.

Kidneys, weight, 195 grams. The capsule slightly adherent, the surface hyperæmic and shows small punctate hæmorrhages. On section contrast between pyramids and cortex diminished, the pyramids paler than normal, the cortex swollen, the normal markings obliterated. Throughout the cortex there are numerous small points and streaks of gray. At the base of the pyramids are numerous small, round or irregular gray areas, most of them from 1 to 2 mm. in diameter, some up to 4 mm. Some of these areas extend as lines to the cortex and occasionally they are present elsewhere in the pyramid than at the base. They often are surrounded by an irregular red zone of vascular injection.

Liver, weight, 675 grams. Of a red-gray color, and both the surface and section show numerous minute opaque, yellow-white points.

The mucous membrane of pharynx congested. The tonsils large, the crypts filled with tough white masses.

All the lymph nodes of the body are enlarged and hyperæmic.

The bone marrow of femur abundant and pale red in color.

The left middle ear contains muco-purulent material.



The gastro-intestinal canal normal save for slight swelling of the lymph follicles. Cultures from the peritoneum, the pericardial cavity and the vegetations on the mitral valve gave pure cultures of streptococci. From the lungs streptococci and pneumococci were obtained.

Microscopical examination of the liver showed scattered circumscribed foci of necrosis, not central and without any relation of situation to the lobule. Large numbers of polynuclear leucocytes were found in the sinusoids and within the cell trabeculae.

The kidneys showed very marked cloudy swelling and fatty degeneration of the epithelium of convoluted tubules. In streaks and in foci there was infiltration of the intertubular tissue with large cells of the lymphoid type. In the foci of such infiltration the cell degeneration was not more marked than elsewhere.

The myocardium in addition to fatty degeneration showed foci of infiltration with cells of the same type as those in the kidney.

**REMARKS.** A death from scarlet fever with an unusual extent of streptococcus infection. The lesions most immediately associated with the scarlet fever are the bronchitis and broncho-pneumonia and the otitis media, which are due to secondary infection. The acute interstitial nephropathy (the pathology of which will be further discussed under "Kidney," page 350) is also a condition not unusual in the exanthemata. There was also streptococcus infection of the blood to which the acute endocarditis, the pericarditis and the peritonitis must be attributed. Infection of the peritoneum originating in other ways than by extension from the intestine or from some other focus is rare, but takes place.

## ACUTE ANTERIOR POLIOMYELITIS

An acute infectious disease with characteristic lesions in the central nervous system. The cause of the disease and the mode of entry of the organism are unknown. Only man and the monkey are susceptible. The virus is filterable and has been shown by the inoculation of animals to be present in the central nervous system and in the mucous membrane of the pharynx. The lesions are inflammation of the pia-arachnoid with serous or sero-hæmorrhagic exudation, degeneration of the gray matter of the cord and infiltration of the tissue with endothelial cells. The vessels of the pia and brain are congested, the perivascular spaces in the brain dilated; there often are hæmorrhages about the vessels. The degeneration and cellular infiltration usually is most intense in the cervical cord, usually involves the entire length of the cord and may affect the medulla and the pons. In these regions there is intense cellular infiltration around the vessels and in the tissue of the gray matter. The ganglion cells are degenerated and often completely destroyed. Polynuclear leucocytes take no part in the process. The endothelial cells come into the region partly by migration, partly from proliferation of the endothelial cells of the tissue. Nuclear figures are found in them. The cells of the neuroglia are swollen, increased in number, the fibrils larger and more conspicuous. Conditions in the main similar to those in the cord are found in the spinal ganglia. There usually is a general hyperplasia of the lymphoid system and acute congestion of the spleen. The disease is more common in children than in adults.

### A CASE OF POLIOMYELITIS

Anatomical Diagnoses. Poliomyelitis; Hyperplasia of lymphoid tissue; Congestion and hæmorrhage of intestine; Chronic hepatitis; Chronic adhesive pleuritis; Congestion of spleen.

Male, white, age five years. Body well developed and well nourished, surface normal.

Peritoneal cavity normal.

Both pleural cavities, but particularly the left nearly obliterated by tough, fibrous adhesions. Cavities contain no fluid.

Pericardial cavity normal.

Heart weighs 90 grams. Normal.

Lungs. Both crepitant throughout.

Liver. Weight 600 grams. On the surface there are small pale depressions, most marked on anterior surface near region of the gall bladder. The edges of liver are irregular. The capsule is thickened.

Gall bladder and ducts are normal.

Pancreas normal.

Spleen, weight, 90 grams. Capsule tense, organ of dark red color.

Kidneys. Combined weight 110 grams. Pyramids somewhat congested.

Gastro-intestinal track. Stomach normal. In the lower portion of the ileum the Peyer's patches are enlarged, elevated, the vessels injected and in some are small areas of hæmorrhage. The solitary follicles also are enlarged and a few foci of hæmorrhage are seen.

Lymph nodes. The mesenteric lymph nodes, especially those of the ileo-cæcal region, are enlarged. The largest of these is 2 cm. in diameter.

Organs of neck not examined.

Brain. Calvarium and dura normal. The vessels of pia mater deeply injected. In places there are small hæmorrhages from 0.2 to 1 cm. in diameter. In places these are so numerous as to become confluent. The hæmorrhages are most marked over the temporal lobe posteriorly. The vessels at base of brain are normal. The pia strips easily. The brain is moist, the small vessels are prominent. The ventricles contain clear fluid, the ependyma is smooth and glistening. In the region of the olivary body on the right side there is a small, pale yellow area about 1 mm. in diameter.

Spinal cord shows lesions of varying extent which are most marked in the cervical region. Here the anterior horns have in part lost their normal outline, in part hæmorrhages are seen in them. The hæmorrhages are usually small and punctate, and are not symmetrical in distribution. The gray matter appears swollen and irregular, the contrast with the white is not so sharp; apart from the hæmorrhages there is a diffused redness. This character of the gray matter extends through all the cord.

**REMARKS.** The lesions of the central nervous system in this case are typical of the disease. Associated with the disease are the hyperplasia of the lymphoid tissue with hæmorrhage and the acute congestion of the spleen. The chronic hepatitis is an unusual condition in a child of this age and very possibly associated with some antecedent infection. Such extensive pleuritic adhesions also are unusual in children.

## PARASITIC WORMS \*

*Cestodes* or *tapeworms* are not uncommon parasites in man; the adult worm inhabits the alimentary canal and the larval forms occasionally invade the tissues. These worms are jointed, they consist of a head or scolex which adheres to the intestinal mucous membrane and joints or proglottides, in which there is hermaphroditic sexual differentiation. By the great number of proglottides which may form the worm may attain a length of ten meters or more. The sexual organs, both male and female, are found in the segment and numerous eggs are discharged from the single opening. The eggs, which are provided with a chitinous membrane, develop into an embryo or onchosphere which, still enclosed in the membrane, is taken into the alimentary canal of a suitable host. This penetrates the intestinal mucous membrane and enters the lymph or blood stream and is deposited in the tissues. There it develops into a vesicle, cystocercus, from some part of which one or numerous scolices are developed. These, when taken into the alimentary canal of the primary host, develop into the adult worms.

Of these worms, three are important, *tænia saginata* or beef tapeworm; *tænia solium* or pork tapeworm; and *dibothriocephalus latus* or fish tapeworm. The worms infest man as their primary host and develop in his intestinal canal, the scolex of the first two being attached by means of both hooklets and suckers and that of the fish worm by means of suckers only. The proglottides of the first two are longer than they are broad, when fully developed, whereas those of the fish worm are broader than they are long. Numerous other differences can easily be made out by minute examination. The fish worm infestation is most serious because

\* It is not possible to discuss fully these parasites in the limitation of space which this treatise demands, and the same is true of the animal parasites generally. Only those animal parasites have been considered which have appeared to the author as most important both in their pathogenic properties and as types. Excellent descriptions can be found in all text books of medicine. Only the most common of these parasites which actually invade the tissues either in the adult or larval form will be discussed here.

the subject may become the victim of a serious anæmia, closely resembling pernicious anæmia and probably caused by the absorption of a hæmolytic lipid found in the segments.

When the onchospheres of *tænia solium* enter the stomach of man, cysticerci cellulosa are found in some organ generally remote from the alimentary canal. In its typical form this is an elliptical vesicle from 1 to 2 cm. in the long and from 0.5 to 1 cm. in the short diameter. In the interior a white point, the invaginated scolex, can be recognized. The membrane of the vesicle is characteristic in its homogeneous refractive structure and its smooth, linear, internal contour. Such cystocerci are especially common in the brain, but may occur in any of the organs. They may occur in great numbers in the muscles or subcutaneous tissue. They produce degeneration and various types of reaction in the tissue about them.

A form of cysticercus known as the echinococcus cyst arises in man as the secondary host from swallowing the onchospheres of the *tænia echinococcus*, a very short tapeworm found in the dog. These cysts may be very large and innumerable scolices may be formed in them. The wall consists of two layers, the outer composed of numerous transparent lamellæ, and an inner so-called parenchymatous layer which is granular and contains glycogen. From this parenchymatous layer small cysts or brood capsules develop each of which may contain numbers of scolices. The fluid of the cyst is colorless or slightly yellow and contains no albumen. The cysts grow slowly in size and may attain large dimensions. They are most common in the liver, but may be found in other situations.

The *Nematodes* or round worms are very common. Some are only rarely harmful, others are of considerable pathological importance. The size varies greatly. The sexes are separate, the male usually is smaller than the female and often has the posterior extremity rolled up. They contain a digestive canal extending from the mouth to the anus. Either ova or embryos are discharged, the latter being sometimes larvæ which undergo a further metamorphosis before becoming worms. Infestation may be direct or by the intermediary of another host.

The *trichocephalus trichiurus* (*dispar*) is a widely distributed parasite. The anterior end is hair-like, the posterior end thickened, and in the male rolled into a spiral. The male is from 40 to 45 mm. in

length, the female from 45 to 50 mm. They are found in the cæcum, vermiform appendix and colon and the anterior whip-like end is embedded in the mucous membrane. It is evident from the iron-containing pigment of the alimentary canal of the parasite that it ingests blood. When in large numbers considerable degrees of anæmia accompany their presence. The frequent presence of these parasites in the vermiform appendix suggests that they may play a rôle in the production of appendicitis, by favoring a more important bacterial invasion through the slight traumas which they produce.

The *trichinella spiralis*, in its adult condition, inhabits the small intestine. The female is from 3 to 4 mm. long and 0.06 mm. in diameter, the male is much smaller, 1.5 mm. long and 0.04 mm. thick. The life of the parasite is short, embryos being produced in from five to seven weeks, after which the adult worm dies. Infection takes place by eating meat which contains the embryos. The parasites are freed from the capsules which surround them and quickly develop into sexual ripeness, fecundation taking place two to four days after infection. The male then dies and the female at once wholly or partly penetrates the mucous membrane. Each female produces as many as 1500 embryos which enter into the lymphatics. A part of them are retained in the mesenteric lymph nodes, but the mass, passed by means of the thoracic duct into the blood, is carried into the striated muscles of the body with the exception of the heart. They are first found within the muscle fibres in an elongated shape and separated from the contractile substance by a clear border. In the further growth they become rolled into a spiral within the fibre. A hyalin capsule in which lime salts are deposited forms around the parasite. The severity of the disease depends upon the number of infecting parasites.

*Ankylostoma duodenale* is the name of the European and *uncinaria americana* the name of the American species of a nematode which inhabits the alimentary canal and produces serious anæmia by blood destruction. In the fresh condition the worm is pale red in color, the male 1 cm. long and 0.5 mm. thick and has on the posterior end a characteristic bursa by which it fastens to the female in copulation; the female is slightly longer and pointed at the posterior end. The eggs, when passed, are generally in the stage of segmentation. The head is provided with sharp teeth or plates by which the worm bites into the mucous membrane and sucks the

blood. The anæmia is due to the loss of blood which is devoured by the parasite, to the slight hæmorrhages which take place from the wounds when the parasite changes its position, and probably to a hæmolytic poison which the parasite produces. Infestation is without an intermediate host. The eggs in water or in moist earth develop into embryos which may be swallowed, or when they come in contact with the skin they penetrate this and enter into the lymphatics or blood vessels. Those in the lymphatics are in part retained in the lymph nodes, in part carried into the blood. By means of the blood they may be carried into the lungs from which they make their way by means of the bronchi and trachea into the œsophagus and alimentary canal.

*Flukeworms* or *Distomata*, the most important of these to man is the *Schistosomum hæmatobium* (*Distomum hæmatobium Bilharzia*). The sexes are separate, the male thicker and somewhat shorter than the female, and is from 12 to 14 mm. long and 1 mm. broad. The sides of the male roll forward over the abdomen to form a gynæcophorus canal in which the female is carried. The mode of infection is not known; the parasite settles in the venous system either in the branches of the portal vein or in the veins of the pelvic organs, as the bladder and rectum. The ova pass from the vessels into the tissue, where they produce a severe inflammation particularly when they enter the tissue of the bladder. They may produce hematuria; urinary fistulæ surrounded by large masses of granulation and cicatricial tissue may perforate the scrotum and rectum. There may be an ascending infection leading to pyelonephrosis. On microscopic examination the ova are found embedded in dense masses of cicatricial tissue. The parasite has an interesting position in view of the frequency of the development of papilloma and carcinoma of the bladder at the site of the bladder lesions associated with the presence of ova.

**EXPERIMENTS.** The experiments in infection overlap those of inflammation so that the student is referred to those on the latter subject for some of the simpler manifestations of infection (see p. 58). For the study of the effects of diphtheria bacilli and their toxin, guinea pigs are to be used. Inject subcutaneously into a guinea pig 0.5 c.c. 24-hour bouillon culture bacillus diphtheria and into another animal 2 units of diphtheria toxin. Observe the clinical course of the condition in both animals; at death perform autopsy

and make histological and bacteriological examinations. The experiment is made additionally interesting by protecting other animals by the use of anti-toxin. Similar experiments with bacillus dysenteriae and its toxin are of value but the protecting influence of anti-toxin is so slight as to be of little value in this form of experiment. The production of "rat typhoid" by the subcutaneous injection of 0.5 c.c. 24-hour bouillon culture bacillus murisepticus shows interesting lesions, which almost duplicate those of human typhoid. The special lesion of pneumococcus septicæmia in rabbits is best studied by the injection of 0.5 c.c. 24-hour neutral bouillon culture of pneumococcus into the posterior auricular vein. The student can get the culture by injecting pneumonic sputum intraperitoneally in the mouse and making cultures from the heart's blood. The same culture can be used for intrabronchial injection into the dog in amounts of 6 c.c. The dog should be killed at the end of 2 or 3 days after close clinical study and the autopsy should include careful histological and bacteriological study. Tuberculosis and syphilis present interesting experimental lesions. Two guinea-pigs should be injected intraperitoneally each with 0.5 c.c. salt solution suspension human type tubercle bacilli and two others with bovine type bacilli. The animals are to be observed clinically until death. The differences in clinical course and findings at autopsy should be noted. The material from a chancre or moist syphilitic condyloma should be injected into the testicle or under the skin of the scrotum of a rabbit. With the appearance of the lesion, smears should be studied, the animal killed, sections of the testicle studied by ordinary histological methods and by the Ghoreyeb and Levaditi methods for tissues.



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## THE PATHOLOGY OF THE ORGANS AND TISSUES OF THE BODY

### INTRODUCTION

Most of the pathological changes in the individual organs and tissues of the body have already been considered in the various topics discussed. With this preceding knowledge and with certain things held clearly in mind, the pathology of the organs should present little difficulty. It is important to bear in mind (*a*) the anatomy of an organ, this including topographical relations, gross form, size, mode of development (the last particularly as affecting malformations), circulation and histological structure; (*b*) the physiology of the organ, in relation to the body as a whole and whether or not its chief function is excretory or secretory; (*c*) the infections to which it may be subjected, including resistance to infection, relations to the outer world as influencing entry of organisms, the relation of structure to internal extensions of infection; (*d*) the character of the degenerations which take place, their situation, mode of origin and tissue reactions; (*e*) the capacity for repair, regeneration and hypertrophy; (*f*) the tumors both primary and secondary which may develop. While there is a close similarity in the pathological changes in all the organs of the body, there are, however, in every organ certain pathological conditions, which, like the organ itself, have individual characteristics. These are more pronounced in the kidney than in any other organ, with the possible exception of the central nervous system, and the pathology of the kidney will be considered not only for the importance which necessarily attaches to the organ, but that the description may serve as a type for the study of organic disease.

## THE PATHOLOGY OF THE KIDNEY

**DEVELOPMENT AND ANATOMY.** The kidneys are paired organs of bean-shape, the combined weight in the adult being 300 grams; they are deeply placed in the abdominal cavity behind the peritoneum and at the sides of the lumbar vertebræ. They lie closely applied to the diaphragm, the right kidney in close relation with the corresponding adrenal gland, the liver, the duodenum, the hepatic flexure of the colon, and to a limited extent to the small intestine; the left in relation to the adrenal gland, the spleen, the stomach, the pancreas, the splenic flexure of the colon and the small intestine. Each kidney is closely invested by a fibrous capsule. From its situation the kidney is well protected from trauma, and there is but little tendency for pathological conditions in neighboring organs to extend by continuity into the kidney. The kidney has a complex development in that two dissimilar tissues take part in the formation of its parenchyma. The ureter, the pelvis, calices and the collecting tubules develop by an outgrowth from the Wolffian duct, the remaining system of tubules from the nephrogenic tissue. The embryonic development is not completed at birth and may continue up to the second year of life. The kidney contains epithelial tubules which pursue a tortuous course and which in their course present differences, in the character of the epithelium, in diameter and in function. The tubules have an average length in the adult kidney of 5.2 cm. and begin with an expanded end into which a mass of blood vessels projects as does the heart into the pericardial cavity. This structure, known as the glomerulus, is covered by a syncytial epithelium continuous with the epithelium of the tubules. The blood vessels of the glomerulus, which in size resemble capillaries, are divided into small groups, the epithelium dipping down into the divisions between the groups. The vessels are lined with syncytial endothelial cells containing scattered nuclei. The space surrounding the glomerulus (the subcapsular space) is covered with low epithelium; both the glomerular and the capsular epithelium are more prominent

in the new-born than in the adult. From the capsular space there opens a tubule convoluted in its course (the proximal convoluted tubule) lined with large epithelial cells without distinct cell boundaries. The nuclei are near the basement membrane on which the cells rest. The cytoplasm is granular, the granules at the base of the cells arranged more or less in lines, and around the lumen there is a brush-like border strongly suggestive of cilia. The convoluted tubule changes suddenly into the descending arm of the loop of Henle in which both the diameter of the tube and the lumen is reduced in size; the epithelium becomes low, the cells separated, the tubule resembling a capillary lined with swollen endothelium. The tubule, after passing toward the pelvis, makes an abrupt turn passing back towards the cortex as the ascending arm of the loop of Henle, which is of larger diameter and lined with larger and more granular epithelium. The ascending limb of the loop passes into a second or distal convoluted tubule which lies in close relation with the glomerulus from which the tubule originated. It is possible on sections of the kidney to distinguish the proximal from the distal convoluted tubule by the larger lumen and the lower and clearer epithelium of the latter. The distal convoluted tubule passes into the collecting tubule, which, after dichotomous joining, opens into the pelvis of the kidney at the papilla.

Certain markings are recognized on section passing through the kidney, due to the distribution in different parts of the kidney of tubules differing in structure. Projecting into the subdivisions of the pelvis, the calices, are the rounded extremities of the pyramids. The pyramids are triangular in shape, are paler, more transparent than the remaining kidney structure and show distinct striæ. At their base they come in contact with the cortex and the pyramidal extensions of the tubules composing them (pyramids of Ferrein) project into the cortex, but the pointed extremities of the latter do not reach the surface of the kidney. Between these pyramidal extensions are the convoluted tubules and the glomeruli, giving the tissue here a more opaque and granular appearance. In the adult kidney the glomeruli can be distinguished with the naked eye as fine red points. The tubules of the kidney are surrounded by a membrana propria composed of fine, resistant fibres, reticulum, which, with its connections, forms a continuous framework throughout the organ. This is more abundant than elsewhere

in the pyramids, around the larger vessels and about the glomeruli. Separating the pyramids of the kidney are masses of cortex, the columns of Bertini which pass down to the pelvis. In the foetal kidney and in the kidneys of certain animals the organ is more or less subdivided by surface depressions into a number of units termed *renculi* each of which comprises a pyramid and its associated cortex. In the adult kidney traces of these sometimes are preserved.

**VASCULAR SUPPLY.** The renal artery breaks up into a number of branches which pass around the pelvis and before entering the kidney each divides into from three to five smaller branches which enter the kidney at the side of the papillæ. These vessels do not anastomose, each supplying a definite area of kidney tissue. On reaching the bases of the pyramids each artery breaks up into a series of branches, the arcuate arteries, pursuing generally an arched course across the bases of the pyramids. From these arches branches are given off which extend to the cortex, and the glomeruli are placed at the extremities of short branches given off from these. From the arches a few branches (*arteriæ rectæ*) also are given off, which extend into the pyramids. The arterial branch (*vas afferens*) entering into the glomerulus, divides into from four to six branches each of which breaks up into bundles of capillaries which may or may not anastomose. These masses of capillaries produce the lobulated appearance of the structure. The capillaries unite into a single vessel (*vas efferens*) which leaves the glomerulus and breaks up into a rich capillary plexus around the tubules. The blood passes from the capillaries by three routes. The capillaries of the cortex pass into small veins beneath the surface of the kidney and running parallel with it, several of which converge at a single point making a stellate figure (*stellulæ Verheyneii*) to form veins which pass through the cortex in company with the corresponding artery. The cortical capillaries also pass into small branches which join the vein as it passes through the tissue. These cortical or interlobular veins pass into the venous arches which accompanying the corresponding arteries. The capillaries of the pyramids pass into straight vessels (*venæ rectæ*) which empty into the arcuate veins. The veins in their further course are without valves, accompany the artery and pass into the vena cava. The lymphatics of the kidney pass into large collecting trunks which surround the renal artery and discharge into lymph nodes along the aorta and vena cava. The blood

supply of the kidney is relatively great. Although the kidneys form but 0.56 per cent of the body weight, in strong diuresis 5.6 per cent of the total amount of blood sent into the aorta in a minute may pass through them.

The function of the kidneys is wholly excretory and nearly the entire nitrogen elimination takes place by the urine; it is also by means of the kidney that toxic substances whether formed in the body or introduced from without are removed, and in the process of removal, by their concentration, may produce important pathological conditions. In the process of excretion it is assumed by most authors that water and salts, especially urea and sodium chloride, are discharged through the glomerulus and in this function blood pressure and rapidity of stream are of prime importance. Various substances introduced into the blood, such as indigo carmin, are discharged by the epithelium of the convoluted tubules and may be demonstrated in the epithelial cells. Methæmoglobin, when present in the blood, is also so discharged. The frequency with which degeneration of epithelium limited to definite areas of the tubules is met with is in favor of the view that there is variation in functional activity in different sorts of epithelium. It also is generally believed that the urine undergoes a concentration in its passage through the tubules by water absorption, the best evidence for this being the concentration of albumin to form casts in the Henle loops, and the formation in the collecting tubules of crystalline products, such as uric acid.

**MALFORMATIONS.** The most common and the least important consist in the retention of the foetal lobulations or of slight depressions in the surface indicating this. Congenital displacements may occur and the dystopic organ lies abnormally low either over the sacroiliac junction or in the pelvis. In these cases the kidney usually is malformed, flattened anteroposteriorly, the pelvis turned to the front,<sup>4</sup> and the artery given from the lower part of the aorta or from the iliac artery. Usually but one kidney is displaced, the left, and the malformation is more common in males. Both kidneys may be on the same side, one below the other, the lower sometimes overlapping, sometimes united with the upper. The lower poles may be joined together across the vertebral column forming a single horseshoe-shaped organ, but with two pelves and ureters, and the vessels may show variations in number and origin.

In all these variations in position the adrenal glands preserve their normal relations. Great importance is to be attached to the imperfect development or the absence of one kidney. In the greatest degree of hypoplasia the kidney is represented by a mass of bean-size with pelvis and attached ureter. Microscopically, tubules without glomeruli are found in the structure, the malformation being due to lack of development on the part of the nephrogenic tissue. In other cases the organ is larger and contains glomeruli and tubules, together with a relatively large amount of connective tissue. The blood vessels are correspondingly small and may have an abnormal origin. It is not impossible that certain of these hypoplastic kidneys may result not from malformation but from intra-uterine atrophy due to insufficient vascular supply. Hypoplasia or aplasia of the kidney is more common in men than in women. The remaining kidney shows compensatory hypertrophy. Among the important malformations are the congenital cystic kidneys which are due to the lack of junction between tubules which are developed from the Wolffian ducts and those which are developed from the nephrogenic tissue, and the accumulation of fluid in the latter. In marked degrees of this malformation enormous organs filled with a multitude of smaller and larger cysts are produced, the size of which may form an impediment to the delivery of the foetus. The cysts always contain constituents of the urine; their contents may be clear or variously discolored by the admixture of blood pigment from slight hæmorrhages into the cysts, or cloudy from products of degeneration of the lining epithelium; many of the cysts contain colloid and mucin. There is increase in connective tissue in the walls of the cysts, but there may be no interference with the function of the kidney. These pronounced cases of cystic kidney frequently are associated with malformations elsewhere. There are transitions between these cystic kidneys and the presence of solitary cysts which may be as much as 8 cm. in diameter and which have a similar origin.

**MALFORMATIONS OF URETERS.** One of the most frequent malformations of the ureters is the double ureter with or without doubling of the pelvis and appearing on one or both sides (page 367). The ureter from the double pelvis may unite before the entrance into the bladder, or the separation may be complete. Malformation of the ureter may take the form of narrowing, or closure, which



occurs at the places of anatomical narrowness, at the origin from the pelvis and before entering the bladder. In the former case the narrowed ureter is given off at an angle high up in the pelvis of the kidney, which becomes greatly dilated, congenital hydronephrosis. A sharp angle at the origin of the ureter may give rise to hydronephrosis without any narrowing of the tube.

Regeneration and hypertrophy of the kidney have already been considered (page 129).

THE NOMENCLATURE of the pathology of the kidney is confusing. The lesions are varied both in extent and in character, and complexities arise due to the complexity of both structure and function. Regarding the essential anatomical units of the kidney, as the glomeruli and the tubules, the one or the other may be chiefly affected which would make possible an anatomical classification and nomenclature, but in numerous conditions both are affected to the same degree. The relations of tubules and glomeruli make this unavoidable, the tubule, in addition to its specific excretory function, serving as the duct of the glomerular gland and when the latter is destroyed the tubule undergoes atrophy. In the same way destruction of tubules entails destruction of the related glomeruli. There is, however, justification in considering certain of the glomerular lesions as a unit, from the fact that they are primary and the pathological changes similar in character. A better nomenclature is one based on ætiology, but apart from the fact that the ætiology, especially of the chronic lesions, is obscure, the same ætiological factor in different degrees of intensity and with a difference in the associated lesions in other organs, can produce various conditions in the kidney. The kidney, being the great organ of elimination, is easily injured in the discharge of toxic substances; in the infectious diseases there may be lesions which are due to the presence of the infectious agents and lesions mainly degenerative in character, which are due to the action of toxins formed elsewhere. The term nephritis (inflammation of the kidney), with a preceding descriptive adjective, has been hitherto generally adopted to designate lesions of the kidney whatever their character. All lesions in the body, so far as they comprise the result of injury and the resulting reaction of the tissues, might be termed inflammation; but the use of the term inflammation has become limited to describe those lesions in which the formation of an exudate is the leading characteristic. If

this criterion be adopted, the term cannot be applied to many of the pathological conditions in the kidney. Bright, an English physician in 1827, described a pathological condition of the kidney associated with dropsy and albuminuria and the name Bright's disease has since been used in an indefinite manner by both physicians and laity to signify pathological conditions in the kidney whether they are or are not associated with dropsy and albuminuria. There is at present a tendency to substitute for nephritis the term nephropathy which signifies disease of the kidney, with a preceding adjective or clause descriptive of the special anatomical or ætiological feature, and this usage will be adopted here.

VASCULAR NEPHROPATHY, i.e., disease of the kidney due to disturbance in the circulation. *Acute hyperæmia* of the kidney occurs in increased functional activity and as a part of many pathological conditions, but in itself leads to no alteration in structure. The condition is well shown in acute cases of poisoning by corrosive sublimate and arsenic. The kidney is swollen, the capsule tense, the color an intense red, the glomeruli easily visible, and blood drips on section. *Passive hyperæmia* (chronic passive congestion) occurs when there is obstruction to venous outflow due either to a local or central cause. The kidney is large, heavy, of a dark or blue-red color and the consistency increased. On section the pyramids are cyanotic and the venæ rectæ appear as prominent blue-red streaks; the glomeruli are easily seen as bright red points. Histologically, there is slight degeneration, and often atrophy of the epithelium, increase in the interstitial tissue which may take the form of thickening of the membrana propria and the glomerular capsules, or occur in foci associated with greater degrees of atrophy. The glomeruli are large, the vessels distended with blood and not infrequently red blood corpuscles are found in the capsular spaces and in the tubules. A few hyalin casts are found in the tubules, and after boiling a slight albuminous coagulum in the capsular spaces and in tubules. The estimation of the effect of passive congestion is made difficult by the frequent presence of conditions due to other factors. Passive congestion rarely is due to local interference with the circulation. Sudden closure of the renal vein produces intense congestion and hæmorrhage, but the closure by thrombus formation or by tumor growth in the vein, produces little or no result, the blood passing from the kidney by collateral channels.

*Infarction* following arterial closure is more common in the left than in the right kidney due to the more obtuse angle of its artery with the aorta. The form and size of the infarct depends upon the character of the occluded artery. When an arcuate artery is occluded near its origin, the infarction is large, very irregular in outline and embraces both cortex and pyramid. The infarct may be confined to the cortex and be more or less rectangular in shape. The healing of the infarcted area, which takes place by organization, leads to depressed cicatrices in which hyalin masses representing the glomeruli are seen. There is no regeneration.

*Hæmorrhage* frequently takes place in the kidney and may be the single or the most prominent lesion. It may take place from the intertubular vessels, or, as usually is the case, from the glomeruli. The hæmorrhages appear as small red foci most numerous in the cortex. In cases where the hæmorrhage is extensive, the presence of the blood in the straight tubules gives rise to red streaks on section.

A special type of nephropathy has been described in connection with arterio-sclerosis, but without reason. Arterio-sclerosis may, in two ways, produce lesions in the kidney; (1) by local interference with nutrition as when single arteries are affected chiefly, foci of atrophy being produced; (2) by more general arterial disease affecting the nutrition of the entire organ and producing diffuse lesions. The arteries of the kidney must be regarded as among the vessels most susceptible to arterio-sclerosis, and may be affected in cases in which there is but little evidence of arterial change in other organs. It is difficult to estimate the rôle which arterial disease plays as a single factor in the production of the associated renal lesions; a large number of other factors may play a part such as the injurious action of substances derived from defective metabolism, the associated high arterial pressure and frequent association of passive congestion.

**OBSTRUCTIVE NEPHROPATHY.** (Hydronephrosis.) Obstruction to the urinary outflow may be produced in several ways. The ureters are long thin-walled tubes and the lumen can be constricted by pathological conditions arising within them or by pressure from without. Obstruction to discharge from the bladder, occurring particularly in man, quickly distends the ureters. Calculi formed in the pelvis of the kidney may become impacted in the ureter, this generally taking place at the entrance into the bladder. External

pressure on the ureter is more common in women owing to the greater frequency of tumors of the pelvic organs, and approximately balances the effect of urethral disease in the male. The obstruction gives rise to dilatation of the pelvis of the kidney and atrophy of the organ (hydronephrosis). Complete obstruction is rare. The greatest degree of hydronephrosis is seen in the congenital cases in which the ureter is inserted high up in the pelvis of the kidney and emerges at an acute angle. The condition usually is bilateral. The pelvis of the kidney may be converted into a sac containing several litres of fluid and the kidney be represented by a thickened area of the sac wall in which, on microscopic examination, atrophic glomeruli and tubules can be recognized. In less marked cases the calices are still present and the atrophic changes are most evident in the pyramids. The atrophy is due both to the effect of pressure on the epithelium and to anæmia due to the compression of the vessels. The kidney is always paler and denser than normal; microscopically, there is atrophy and degeneration of glomeruli and epithelium and a general increase in the interstitial tissue which is rich in elastic fibrils. There is also both general and focal infiltration with lymphoid cells. By infection, which readily takes place, suppuration of the pelvis and kidney may be produced, converting the hydronephrosis into a pyelo-nephritis.

The formation of calculi in the pelvis of the kidney, *nephrolithiasis*, is due to the precipitation from the urine of uric acid or salts. The calculus formation is assisted by products of inflammation and degeneration, forming a nucleus on which the sediment accumulates. The calculi may be single or multiple and vary in size from that of fine sand to large branching structures representing casts of the entire pelvis and calices. The formation may take place in single calices.

**INFECTIOUS NEPHROPATHY.** The infectious lesions of the kidney are focal and the organisms may reach the organ by the blood or urinary tract, the lesions in the different cases showing anatomical variations. The pelvis may share in the infection, *pyelo-nephritis*. The types of the infections of the kidney are those by the pyogenic organisms and by the tubercle bacillus; these have already been considered.

**DEGENERATIVE NEPHROPATHY.** Degeneration of the epithelium of the kidney is found in all types of lesions and may constitute the

only injury apparent. Most forms of degeneration which occur in man may be produced experimentally in animals. The degeneration may affect to an almost equal degree all parts of renal parenchyma or be confined to certain areas in the tubules. In many cases the degeneration in the kidney seems merely to share in the general degeneration of the tissue due to the circulation of an injurious substance, in others the degeneration is so much more marked in the kidney that we must assume either a greater vulnerability of the cells of the kidney, as compared with other organs, or a concentrated action of the agent such as is associated with its elimination. It is known that arsenic and other substances are excreted by the kidney and in diphtheria the specific toxin is found in the urine. Degeneration in general is most marked in the epithelium of the convoluted tubules, which is in accord with their known secretory activity.

Normally, the human kidney contains no fat demonstrable by microscopic methods, the comparatively large amount of fat which chemical methods show being so combined with protein as to be incapable of demonstration by other than chemical methods. The fat which normally is present in the kidney of the cat is confined to the convoluted tubules and the ascending division of Henle's loop. In *fatty degeneration* (see page 29) of the human kidney the fat may have either a systematic or irregular distribution. In the former it may be confined to the glomerular epithelium, to that of the convoluted, Henle or collecting tubules. It often is present in considerable amount in the epithelium of tubules which in chronic disease undergo compensatory hypertrophy. In arterio-sclerosis the fat may be irregular in distribution owing to the varying degree of the affection in different arteries. In the infections, also, fat may have a focal distribution, the degeneration being associated with the focal action of the infectious agent. The fat is in small granules, generally near the basal border of the cells, may constitute the only apparent alteration, or may be associated with advanced alterations, complete necrosis and desquamation. Rarely, it may occur in large masses, the affected cells resembling fatty liver cells. Macroscopically, the presence of fat gives rise to a general pallor and greater opacity either of the entire kidney or of the areas of irregular distribution. In *cloudy swelling* (see page 29), the cells are swollen and the granulation more evident than normal. The condition is

always most evident in the convoluted tubules, but not confined to these. It often is associated with other evidences of injury, such as broken or irregular contour of the cells, desquamation and abnormal nuclear staining. The condition underlying this visible alteration in the cells is unknown, as for example, whether it represents an increase in number, swelling or other change in the normal granules, or precipitation in granular form of substances previously in solution. Alone it probably represents a slight degree of cell injury. Closely related to this is the formation of large, round hyalin droplets in the cells, associated with great swelling and disintegration, in consequence of which the hyalin material may accumulate in large masses within the tubules. The degeneration is a serious one and is confined to the proximal convoluted tubules. It occurs in those forms of nephropathy in which the glomeruli are affected chiefly. In *amyloid degeneration* (see page 31), the amyloid substance is deposited chiefly around the vessels. It is associated with other forms of degeneration, particularly the hyalin degeneration of the convoluted tubules, and when formed rapidly and in the absence of atrophic and sclerotic conditions of the kidney, produces a very characteristic macroscopic appearance. The kidney is very large, in the adult the combined weight often reaching 600 grams. It is pale, the stellate veins prominent; on section the cortex is greatly swollen, the markings obscure, and there usually are foci of opacity due to the presence of fat. The increased size is due to a combination of epithelial swelling, dilatation of tubules and interstitial oedema and the general pallor to the inhibition of the circulation brought about by the deposit of amyloid in the walls of the vessels, particularly in the glomeruli.

Various substances may be excreted by the kidney in such amounts as to be insoluble in the urine and deposited in the tissue. The best example of this is seen in the *uric acid infarction* of children. This occurs almost regularly in the kidneys of children newly born or a few weeks old, more rarely in the first years of life and very rarely in adults. In this condition there are closely set golden yellow streaks in the pyramids due to the deposit in the papillary ducts of round or irregular granules of uric acid which often show concentric or radiate markings. In these cases uric acid in sand-like particles may be present in the pelvis or in the calices. In cases of gout there may be deposits of needle-shaped

crystals of urate of soda, the crystals radiating from an apex which points in the direction of the pelvis. The masses often are surrounded by necrotic tissue and giant cells. In jaundice of newly born children (*icterus neonatorum*) there may be crystalline deposits of bile pigment in the pyramids of the kidney, *bilirubin infarction*, which simulate the uric acid deposits but are of deeper red color. In jaundice of adults there is always fatty degeneration due to the toxic action of bile salts, which may reach a high degree and be associated with other forms of degeneration and necrosis. The general green-yellow color of the kidney is due to the diffusion of the bile coloring in the tissue, but in addition to this the microscopic examination shows granular masses of pigment in the epithelial cells and contained in the lumina as casts. The pigment also is found in the epithelial cells of the glomerulus and capsule showing that it is excreted in part at least by this structure. In hæmoglobinæmia the dissolved hæmoglobin is excreted by the kidneys and appears in the urine (*hæmoglobinuria*, *methæmoglobinuria*). The excretion takes place through the epithelium of the convoluted tubules which contain beaded masses of hæmoglobin easily recognized on eosin staining, and the same material is found in the lumina. The presence of the hæmoglobin gives macroscopically a rusty brown color to the cortex with brown streaks in the pyramids due to hæmoglobin casts in the collecting tubules. As elsewhere in the body necrotic tissue in the kidney can become calcified, but it is not common. It takes place especially in the necrosis of epithelium which is produced by poisoning with corrosive sublimate. In cases of increased lime absorption, particularly in old individuals, circumscribed foci of lime salt deposit may appear in the cortex associated with necrosis. Associated with all these conditions there may be a greater or less degree of necrosis. Save in the case of the circumscribed areas of necrosis seen in the infections and in infarction, this takes place in the direction of the tubules. The necrotic cells may show various changes due to degeneration preceding necrosis, or, as in the infarction, a rapid necrosis may produce but little change in the appearance of the cells. Often single cells in the course of a tubule show necrosis. Desquamation of degenerated and necrotic epithelium takes place in varying degree and the castoff cells appear in the urine often in such numbers that the term *desquamative nephropathy* has been used to distinguish

such cases. After death changes in the kidney take place quickly, and in handling or sectioning the kidney, the epithelium of the collecting tubules may become exfoliated in large masses and appear in the lumen as a convoluted mass of adherent columnar epithelial cells and be mistaken for a pathological condition.

**ALBUMINURIA AND CASTS.** The most constant clinical evidence of pathological conditions in the kidney is given in the presence of albumin in the urine, although there may be extensive alteration in the kidneys without albumin and the albumin in the urine may come from elsewhere than the kidney. It is probable that its presence, even in the cases of the so-called physiological and in the transient albuminuria, is indicative always of some lesion although examination may not reveal it. In cases of albuminuria when the kidney is boiled and frozen sections made, coagulated albumin is found in the capsular space of the glomeruli and it is generally assumed that the albumin of the urine has entered this by means of the glomerulus. It may, however, be due to an exudate or transudate which passes from the interstitial tissue into the tubules. With the albumin structures termed *casts* usually appear in the urine. These are cylindrical in shape, varying somewhat in diameter (11 to 22 $\mu$ ), and are composed of a homogeneous hyalin material often containing other substances. The hyalin material varies in appearance sometimes having such slight density and refraction as to be seen with difficulty, at others it is dense, refractive and the casts often show fissures as though produced by partial fracture. These two sorts of hyalin material have a different origin. The pale transparent *hyalin casts* represent albumin which has become concentrated by absorption of water in passage along the tubule and has undergone some form of colloid change. Elsewhere in the body, as in the lungs, hyalin substances of this nature are found. The other, more refractive form of cast *waxy cast*, is formed from the hyalin globules of the epithelium, which pass into the tubules. This form of cast appears in the urine in those forms of nephropathy in which such a degeneration occurs, as in amyloid disease, and in other conditions in which the glomeruli are seriously affected. In passing through the tubules other substances can become associated with the hyalin. *Granular casts* are due to the mingling with the hyalin of granules coming from the partial or complete disintegration of degenerated cells. *Fatty casts* are due to



the presence in the hyalin of fat from cells which have undergone fatty degeneration. *Epithelial casts* are those which contain degenerated and desquamated epithelial cells. *Blood casts* contain red blood corpuscles. *Fibrin casts* are those in which threads of fibrin demonstrable by staining, appear when there is a fibrinous exudate in the tubules. The presence of a few hyalin casts in the urine may indicate but a slight degree of lesion persisting in kidneys fully adequate for function and the casts and albumin may be absent in kidneys in which incompetency of function has been produced by extensive loss of parenchyma, those portions of the kidney which are functioning, but inadequately, being normal.

**ACUTE DIFFUSE NEPHROPATHY.** The degenerative conditions which we have been considering may be extensive and combined with other diffuse lesions consisting in vascular changes and exudate formation; but these affect no part so specifically as to warrant a special designation. The condition is relatively rare, for apart from the infections and the acute interstitial lesions which will be discussed later, acute nephropathy usually is glomerular in character. Certain of the more severe degenerative types, associated with hæmorrhage and exudation, which are seen in diphtheria, belong in this class. It may occur also in typhoid fever, in severe malaria and in streptococcus infection. The lesions are diffuse and vary in character. There is degeneration, necrosis and desquamation of epithelium, with œdema, hæmorrhage and cellular infiltration, in which endothelial cells may predominate, in the interstitial tissue. There may be hæmorrhage and even a fibrinous exudation from the glomeruli, with necrosis of single loops of vessels. Macroscopically, the kidneys are swollen, the markings of the cortex obscure.

**ACUTE INTERSTITIAL NEPHROPATHY.** This is the most common lesion of the kidney in the acute infectious diseases of children, particularly scarlet fever and measles; less common in uncomplicated cases of diphtheria and in smallpox. In adults the condition is more rare, apparently because of the greater rarity of the diseases with which the condition in the kidney is associated. Macroscopically, the kidneys are swollen, often greatly so, pale and mottled on the surface, on section moist, opaque, the markings obscure; abundant cloudy fluid can be expressed. The entire kidney may be affected, or the lesions have a more focal distribution giving rise to streaks of opacity in the cortex. Microscopically, the lesion consists in

infiltration of the interstitial tissue with large mononuclear cells of an indefinite type, often closely resembling or identical with plasma cells, often closely resembling myelocytes. In the most marked cases, all parts of both cortex and pyramids may be infiltrated with these cells; in less marked cases the foci are chiefly in the upper portion of the pyramid, the bordering cortex and around the glomeruli. Some of the large mononuclear cells are eosinophilic; there are also phagocytic cells and a varying number of polynuclear leucocytes. In the capillaries and small veins numbers of similar cells are found, and the source of the cells in the interstitial tissue is by emigration from the blood vessels, augmented by active cell division. The large mononuclear cells are actively amoeboid. They may be found in the walls of the vessels in the act of migration; and in the interstitial tissue they show blunt processes and other morphological evidences of amoeboid activity. Numbers of cells in nuclear division are seen both in the capillaries and among the interstitial cells. The presence of these cells in the interstitial tissue is not in association with epithelial degeneration. Degeneration of the epithelium is present, but not more marked in the interstitial foci than elsewhere, and extensive degeneration and necrosis of epithelium may be present without the interstitial changes. Except in the most marked cases, in which there is associated destruction of tissue, the interstitial cells do not enter into the tubules or appear in the urine. In cases in which these interstitial lesions are found, lesions similar in character often are found in the heart, adrenal glands and elsewhere. There are no lesions in the glomeruli, and although similar cells may be found within the glomerular vessels they do not migrate. The cell accumulations in the vessels and interstitial tissue seem to depend upon changes in the blood. Similar cells, in the diseases concerned, are formed in the spleen and lymph nodes, from which organs they enter the blood. They tend to accumulate in the vessels of the kidney and particularly in those of the pyramids. The great numbers of cells within these vessels shows that they accumulate there, for the circulating blood contains no such numbers. Whether their accumulation is due to some physical condition of the circulation or whether there is a chemotactic attraction is uncertain, but probably the latter is the case, because in spleno-myelogenous leukæmia there is no tendency for the blood cells to accumulate in the kidney.

**GLOMERULAR NEPHROPATHY.** (Parenchymatous nephritis.) As has been said, the glomerulus has the characteristics of a gland, being composed of vessels membrana propria and superimposed epithelium. The wall of the capillaries of the glomerulus is thicker and more refractive than the walls of vessels of similar size elsewhere which are composed of cells alone, and the wall stains as does the membrana propria of the tubule. The embryonic development of the glomerulus by the ingrowth of vascular loops into a tubule lined with epithelium resting on membrana propria is in favor of this view of the vessels, as is the further fact that emigration of leucocytes does not take place through the glomerular vessels save in unusual conditions. The glomerulus has under both physiological and pathological conditions, a certain independence of position, although the dependence of the circulation of the kidney on the integrity of the glomerulus causes degenerative lesions of the tubules to follow lesions of the glomerulus. The glomerular lesions have a further interest in that certain of them are of a character which is not met with elsewhere. The glomeruli may form the initial point of hæmatogenous infection of the kidney, but such infections have no special features. Thrombi due to conglutination of red corpuscles are found more frequently in the glomeruli than elsewhere, for which no explanation is available. The lesions of the glomeruli may be acute, subacute and chronic, with a very indefinite separation of these temporal divisions. The causes of the essential lesions of the glomeruli are substances in solution in the blood and the glomeruli, being equally exposed, all are affected with but little difference in degree. Such substances are formed in the infections and there is a close relation between infectious diseases and glomerular lesions. In certain infections, as in typhoid fever, cerebrospinal meningitis, acute pneumonia, glomerular nephropathy is rare and it occurs more frequently in association with endocarditis than in association with disease of any other organs.

**ACUTE GLOMERULAR NEPHROPATHY.** (Acute parenchymatous nephritis.) This may produce but little macroscopical alteration, save slight swelling. On close examination, however, the glomeruli appear as prominent small opaque points, in very marked cases the section appearing as though sprinkled with fine sand. On microscopical examination the glomeruli are large and filled with cells. The cells have two sources. In one, *intracapillary glomerulonephrop-*

*athy*, the cells are contained within the vessels. In certain cases the individual cell outlines cannot be distinguished and the cells appear as a syncytium. In other cases most of the cells are free within the capillaries. They are of an endothelial character which is apparent both from their appearance and from the presence of nuclear figures in the endothelial cells of the vessels. The newly formed cells do not migrate from the vessels. Cases may be found in which there is also accumulation of polynuclear leucocytes in the vessels of the glomeruli and passage of both these and red corpuscles into the capsular space. The accumulation of cells may be so great that no red corpuscles can be demonstrated within the tufts. Necrosis and rupture of the vessels with resulting hæmorrhage and fibrin in the capsular spaces also may take place. The other source of the cells is from proliferation of the epithelium, both that covering the vascular tufts and lining the capsular space, *capsular glomerular nephropathy*. This is unlike the intracapillary form since it does not occur alone, and is more common in the less acute cases. The covering cells of the glomerulus enlarge, often forming projecting masses of cytoplasm connected with the vessels by a stalk, and extending in masses between the tufts of vessels. The proliferation of the epithelium lining the capsule produces masses of flattened or crescent-shaped cells, the individual outlines of which often are indistinguishable. In sections passing through the attachment of the vessels of the glomerulus, the cell mass in the capsule has a crescentic shape, and in sections showing a part of the glomerulus only, they appear to surround the mass of vessels. The epithelium of the tubules is degenerated, often desquamated to a considerable extent and the lumina may contain desquamated cells from the tubules and crescentic cells from the proliferated epithelium of the glomerular capsule. However, in the acute cases of this form of nephropathy, epithelial degeneration is not so prominent as in many of the more strictly degenerative forms. In the interstitial tissue there may be nothing more than a slight oedema.

**SUBACUTE AND CHRONIC GLOMERULO-NEPHROPATHY.** (Chronic parenchymatous nephritis.) From the acute there is a gradual transition to the chronic forms, in which atrophy is the leading characteristic. The atrophy of the glomerulus takes place by hyalin degeneration of the cells. Even in the acute cases, areas in the

glomerulus are found in which the cell outlines are indistinguishable; in chronic lesions this increases in extent, the cells gradually becoming converted into hyalin masses, the nuclei first shrinking, and finally, for the most part, disappearing. With the hyalin formation and due probably to shrinkage, the lobulation of the glomerulus becomes more evident, it being converted into definite hyalin lobes separated by deep depressions. The hyalin material stains as does the connective tissue, but it is not fibrillar. The mass of proliferated capsular epithelium can undergo the same hyalin transformation, but in this, definite connective tissue fibrils appear, which may be due to the wandering of fibroblasts into the cell mass, or what appears more probable, to their formation, independent of cells. The epithelial cells in the capsule are often arranged around spaces seemingly representing attempts to form tubules. This is due to the tendency of cells, normally lining spaces, to arrange themselves when proliferating, in a manner which conforms to the normal type. At the completion of the process of atrophy, the glomerulus is converted into a mass of hyalin with a few nuclear remains and with a complete absence of vessels. In specimens which are uninjected, all these degrees of glomerular change give a deceptive impression of absence of vessels. The kidneys are injected with difficulty and in all conditions the circulation within the glomerulus is greatly impeded and the vessels in large measure occluded. An imperfect circulation is maintained by the dilatation of short loops at the root of the glomerulus forming communication between the afferent and the efferent vessels, and by new communications which are formed between the vessels of the glomerulus and those of the capsule. In certain cases on the outside of the hyalin masses, numbers of intact vessels may be seen which probably represent a regenerative new formation. Both the macroscopic and the microscopic appearance of the kidney depends upon the chronicity of the process and the degree of atrophy. In the less chronic cases the kidney is enlarged and pale, but the pallor is never so marked as in the large, white kidney of amyloid disease. The combined weight may vary from 350 to 500 grams, but such great enlargement as the latter figure is rare. On section the kidney is firm, the cortex swollen, pale, or mottled, the markings obscure and the tissue more moist than normal. Microscopically, the

lesions are diffuse, all parts of the cortex being equally involved. The most marked condition of the epithelium is atrophy. The cells of the convoluted tubules lose their characteristics and are converted into a low epithelium. The tubules are dilated, but due to the atrophy of epithelium, the dilatation is more apparent than real. The pallor is due to anæmia and may be added to by fatty degeneration of the epithelium. Hyalin degeneration of the epithelium of the proximal convoluted tubule is rarely absent. The tubules are more widely separated by œdema, the normal injection of capillaries is absent save in foci. There is little or no increase in the general connective tissue of the kidney save in the chronic cases where the atrophy is more extreme. Where the glomeruli are completely destroyed the appertaining tubule is collapsed; it may be represented by a small mass of atrophic epithelium or totally disappear. The areas of connective tissue represent for the most part areas of complete destruction of glomeruli and tubules. In the chronic cases, the kidney is small, always rather pale, the capsule may be adherent and the surface smooth or irregularly roughened. On section both cortex and pyramids are atrophic. In these cases the destruction of glomeruli has reached an extreme degree. Both the macroscopic and the microscopic picture of these kidneys may be affected by the presence in the kidney of lesions to which those of glomerular nephropathy are superadded, or which may develop in the course of the glomerular disease. In adults one of the most frequent complicating conditions is arterio-sclerosis with its accompanying renal lesions. The clinical picture of glomerular nephropathy is nearly as characteristic as the anatomical. There is usually the history of an acute onset accompanying or following an infection. Certain of the chronic cases in the adult can be traced to infection in childhood. There frequently are exacerbations of the disease at intervals. The urine is diminished in amount and casts of all varieties are abundant. It is with this form of renal disease that dropsy is so frequently associated. Obscure as is the ætiology, there is such unity in character of the glomerular lesions that it seems most probable, in spite of the number of different infections with which the process is associated, that one single cause must be operative.

**CHRONIC DIFFUSE NEPHROPATHY.** (Chronic interstitial nephritis; granular contracted kidney; gouty kidney.) As is apparent,

by the various synonyms, a dominant feature in this form of nephropathy is atrophy of the kidney. The capsule usually is thickened, and the kidney often is embedded in a large mass of fat. The capsule adheres to the surface in places, and small portions of parenchyma may be torn off with it. The surface may be smooth, but usually is covered with small elevations which vary in size. The general color of the surface usually is red or grayish red, and the elevated granules are redder than the depressions between them. The consistency of the kidney is tough, in some cases almost like leather. On section the atrophy is most marked in the cortex. The markings of the cortex are not apparent and the differentiation of cortex and pyramid not so evident as normally.

Microscopically, the most obvious condition is atrophy of the parenchyma with a marked increase in the connective tissue. The areas of atrophy correspond to the gross depressions on the surface. On section these are triangular in shape, the apex pointing toward the pyramid. The depressed areas may appear as little more than scars, in which the tubules have disappeared and the glomeruli, as small hyalin masses, persist in the cicatricial tissue. The number of cells in the interstitial tissue varies greatly. In the most marked foci and beneath the capsule, there frequently is an intense infiltration with lymphoid cells. Elsewhere throughout the kidney, particularly in the vicinity of the veins, such areas of lymphoid infiltration may be prominent. Cysts are numerous and vary in size, sometimes apparent on microscopic examination only, and filled with stiff colloid material. Towards the pyramids the collecting tubules often are dilated and may have a spiral course due to contraction of the tissue. There is a minor degree of atrophy and interstitial increase in the areas which correspond to the surface elevations. Not infrequently intact glomeruli larger than the normal, some of them reaching  $275\ \mu$ , in diameter, are seen, and in association with them are found convoluted tubules of greater diameter, and greater length, lined with large epithelial cells. Such areas are to be attributed to compensatory hypertrophy of both tubules and glomeruli. Hyalin casts are frequent in all the divisions of the tubules. A varying degree of fatty degeneration always is present together with very marked atrophy of the epithelial cells, and in places there is necrosis. In the more atrophic areas of the kidney, collapsed tubules or tubules containing remains

of epithelial cells can be distinguished. The process of atrophy is different in glomerular nephropathy, although the final result is the same; the atrophy of glomeruli in diffuse nephropathy often appears to be concentric and due to a gradual sclerosis and thickening of the capsule. In most cases, however, the vessels of the glomeruli show a hyalin thickening usually not diffuse, but in foci, and more apparent in the centre of the glomerulus than elsewhere. This takes place with no increase in the number of cells. Occasionally, kidneys are found in which the lesions are less advanced and in which the thickening of the vessels of glomeruli is the most marked feature. The size of the kidney may give but little indication of the degree of atrophy. The atrophy may be concealed by hyperplasia of the fat of the pelvis which takes the place of the renal tissue. Chronic diffuse nephropathy is essentially a disease of individuals past the middle life. Very rarely the condition is encountered under the age of twenty-five years and may even be seen in children, but in these cases the condition is one of minor degree.

**ASSOCIATED CONDITIONS.** The anatomical picture which the kidney presents can be complicated by the association of other conditions such as amyloid, extreme degrees of acute degeneration, and acute and chronic glomerular changes. The essential conditions in the kidney are degeneration, atrophy, connective tissue increase and contraction. The degree of actual increase of connective tissue is difficult to estimate. Frequently in the place of definite fibrillar connective tissue, a hyalin material is formed which stains as does connective tissue. Such material is found more frequently in the pyramid of the kidney than in the cortex. The connective tissue seems to represent more the collapsed framework of the organ than an actual new formation.

**ARTERIO-SCLEROSIS OF KIDNEY.** The most striking single condition in the kidney is that affecting the arteries. Arterio-sclerosis of the larger vessels is almost universally present. The efferent vessels of the glomeruli show hyalin thickening of the walls which can lead to complete closure. The changes in the glomeruli themselves seem to be of much the same character as the arterio-sclerotic changes. The vascular lesions of the kidney, are, however, so much more pronounced in these cases than vascular lesions in other organs, that it is difficult to say whether they should be regarded as primary



or as associated lesions. That the condition is not entirely dependent on arterio-sclerosis is evident from the fact that it may be found, although rarely and in minor degrees, in cases before the arterio-sclerotic age is reached and in which the connective tissue increase seems simply to follow degeneration and destruction of tubules. The condition is essentially chronic and usually only advanced cases are seen. It is not preceded as are the glomerular cases by acute stages. The clinical picture has always been recognized as differing from the glomerular nephropathy. The urine is increased in amount. Albumin is present, but the amount is usually not great. Heart hypertrophy and increased blood pressure is almost uniformly present. Œdema is not usually present, but there may be associated cardiac œdema due to dilatation and insufficiency of the heart. The condition on the whole is not so unfavorable as is the glomerular nephropathy owing to the fact that the lesions are not so diffuse and that the destruction of parenchyma can, to a certain extent, be compensated by hypertrophy of both glomeruli and tubules. The closely related senile nephropathy has already been considered.

#### A CASE OF CHRONIC GLOMERULAR NEPHROPATHY

**Anatomical Diagnoses.** Chronic glomerular nephropathy; Healed operation wound (decapsulation of kidney); Anæmia; Hyperplastic bone marrow; Peritoneal adhesions; Slight hypertrophy of heart; Slight arterio-sclerosis; Malnutrition; Slight œdema of face.

**Clinical history.** Scarlet fever at one year of age and whooping cough at four. Was first seen by a physician July 10, 1905. For one year had had œdema, headaches, loss of appetite, debility, pallor, and had lost weight. On July 18, 1905, by operation through loin, both kidneys were decapsulated. The capsule of the kidney was found thin and the kidney under no tension whatever. They were nearly twice the normal size, mottled and yellowish in color. A piece of the kidney removed at this time showed a subacute glomerular nephropathy. Convalescence was easy and operation led to improvement of all conditions. For two years after the operation there was no œdema of the face and only slight œdema of legs. Appetite also improved, and all bodily functions seem good. Complexion continued pale with a tinge of yellow. Two years after operation condition gradually became worse. There was general weak-

ness, loss of appetite, oedema of legs, but not of face, nausea and vomiting. Toward the end there were convulsions, in one of which she died. Death took place March 10, 1908, two years and eight months after the operation. The urine examination showed before the operation a daily amount of 1440 c.c.m., of high color, slight trace of chlorides, specific gravity 1014, acid reaction,  $\frac{1}{4}$  per cent albumen, large amount of sediment in which were various sorts of renal epithelium, most of them fatty, large hyalin and granular casts and some blood. After the operation, the urine diminished temporarily, but gradually rose in about six months to 2000 c.c.m. which was continued until towards death when the amount was again reduced. The casts were always present and there was always albumen. Three weeks after operation there was only a trace, but this increased in amount and in six months it regained the former  $\frac{1}{4}$  per cent.

White, female, age seventeen years. The body small, slightly built, nutrition poor. No palpable lymph nodes. The general surface of body pale. In each lumbar region there is an oblique linear scar of the old operation wound, each 10 cm. in length. The scar begins 3 cm. below the costal margin, 5 cm. from median line and extends obliquely downwards and outwards. Scanty development of axillary and pubic hair. There is slight oedema of face and eyelids, no oedema of extremities or trunk. The subcutaneous fat small in amount and very yellow.

Diaphragm in usual position. Little fat in great omentum. Mesenteric lymph nodes visible, but not enlarged. The appendix 10 cm. long and free from adhesions. The bladder is distended. It fills the pelvis and reaches to a point midway between umbilicus and pubis. A dense band of adhesions extends from the posterior parietal peritoneum over the right kidney to the inferior surface of the right lobe of the liver, 3 cm. to the right of the gall bladder. There are no adhesions elsewhere. There is no free fluid in the peritoneum. The intestines are collapsed.

The pleural cavities dry and free from adhesions.

The pericardium normal. Over the epicardium of the right ventricle there is a small opaque patch of pericardial thickening.

Heart, weight, 275 grams. The right side is dilated with fluid blood, the left is firmly contracted. On section the myocardium is pale and of normal consistence. Endocardium and valves normal. Coronary arteries normal.

The lungs are normal. There is no oedema.

Liver weighs 1400 grams. The surface is smooth except for a band of adhesions mentioned. The lobules of the liver distinct.

The gall bladder is thin-walled and contains 50 c.c. of dark fluid bile.

Spleen weighs 70 grams. Normal.

Pancreas normal.

Gastro-intestinal canal normal.

Adrenals normal.

The kidneys of the same size, general appearance the same. The right kidney is surrounded with dense tissue containing small quantities of fat enclosed in dense connective tissue. Beneath this the organ has a nodular, rough surface; the capsule is very thick. It strips with some difficulty owing to adhesions with the kidney and leaves a coarsely granular surface. The kidney is pale, opaque, with very small white foci. On section the general cut surface is pale, but the middle is slightly darker than the cortex. The average measurement of the cortex is 3 mm., and on section the glomeruli stand out prominently as pale or pink dots. They are more prominent and larger than normal. There are irregular areas and streaks of pale yellow opacities which are especially marked at the bases of the pyramids, the streaks often extending into these. The cortex shows a fine mottling owing to the presence of pale, opaque, slightly yellow areas. The pelvis is small and contains a small amount of fat; the mucous membrane pale. The renal artery is of small calibre. The ureters small and collapsed. Their mucous membrane, as well as that of the bladder, is pale and smooth. Genitalia normal.

Throughout the aorta there are discrete, slightly elevated patches which are more opaque than the general intima. This is especially marked about the commencement of the intercostal vessels.

Bone marrow is hyperplastic and of light pink color.

Microscopical examination of the kidney stained for fat shows an irregular distribution of this. The largest amount is present in foci of convoluted tubules. The fat is in both the epithelium and in the interstitial tissue. There is fat also present in the glomeruli. In the completely hyalin glomeruli there is a small amount of fat in very minute granules in the hyalin material. Other glomeruli show fat in the thickened capsular epithelium.

A section of the kidney through the capsule showed a greatly thickened capsule composed of cicatricial connective tissue containing but few cells, the fibres of which intermingle with the connective tissue of the kidney. The glomeruli are all greatly enlarged. Most of them show the same condition. On measurement they vary from 275 to 350  $\mu$  in diameter. Most of them are larger than this. As a rule, they do not completely fill the capsular space which contains a considerable amount of granular material. The capsules are thickened. A number of the glomeruli are small, completely atrophic, forming hyalin masses which have fused with the greatly thickened and hyalin capsule. There is every gradation between these completely hyalin glomeruli and glomeruli which

show a development of hyalin within the vascular tufts and a thickened but nonadherent capsule. Occasionally, there are adhesions and vascular connections between the tuft of blood vessels and the capsule. The lobulation of the glomerulus is much more distinct. In each one there are large single tufts of vessels which vary in size, the divisions extending down to the origin. In sections stained with the connective tissue stain, there is general thickening of the walls of the vessels in these tufts and in places a complete substitution of hyalin connective tissue for the vessels. The nuclei are increased in number, the hyalin material often contains great numbers of nuclei. There are numbers of leucocytes contained within the vessels of the glomeruli which are still pervious, but the general cellular increase is in the form of larger cells with nuclei of endothelial character. There is a varying degree of capillary obliteration. In many of the glomeruli the vessels immediately on the periphery bordering the capsule are pervious, their walls of ordinary character and contain red blood corpuscles.

The proximal convoluted tubules in places have a high granular epithelium containing hyalin droplets. Foci of convoluted tubes are found which are dilated and lined with granular epithelium. Casts are numerous in all of the varieties of tubules. The interstitial tissue generally is increased in amount. The membrana propria of the least altered tubules are thickened and in places there are large areas composed almost entirely of connective tissue. Closer examination of these areas shows in the midst of the masses of connective tissue atrophied tubules represented by not more than a few cells. Most of the apparent connective tissue increase seems to be relative and due to atrophy and destruction of parenchyma. There are great numbers of cells in the atrophied tissue.

**REMARKS.** In this case there is a history of acute infection at an early age. The date and the character of the onset of the acute nephropathy is uncertain. There may have been an acute attack coincident with the scarlet fever or whooping cough, with partial recovery and exacerbation, or the nephropathy may have been independent of this. It is of great interest that the operation enabled the condition of the kidney to be ascertained nearly three years before death. This operation is for two purposes: (1) To relieve a supposed condition of increased tissue pressure within the kidney by splitting the capsule; (2) To increase the circulation within the kidney which is obstructed by the glomerular changes by causing a closer connection between kidney and capsule with

anastomosis between the capsule vessels and the renal capillaries. There is no doubt that the adhesions between capsule and kidney in condition of chronic nephropathy may provide increased circulation. In this case it seems to have done good. The convulsions of the patient which preceded death were uræmic and the exact relation of such convulsions to the nephropathy is imperfectly understood. There was a slight degree of heart hypertrophy, and the œdema which was so evident during the course of disease had almost disappeared at the time of death.

#### A CASE OF INTRACAPILLARY GLOMERULAR NEPHROPATHY

**Anatomical Diagnoses.** Intracapillary glomerulo-nephropathy; Anasarca (general); Hydrothorax (double); Ascites; Congestion and œdema of lungs; Arterio-sclerosis (moderate); Fatty liver (slight); Œdema of brain.

White, male, forty-six years of age. Body well developed and well nourished. Rigor mortis. There is very marked œdema of face and in a less degree of the extremities. The conjunctivæ œdematous. The subcutaneous tissues are œdematous throughout.

**Peritoneal cavity.** The peritoneum is somewhat thicker than normal and contains yellow fat; is quite œdematous. The cavity contains 1000 c.c. of fluid. The appendix is 4 cm. in length, has a mesentery to its tip and is directed to the right along the lower wall of the cæcum.

**Pleural cavities.** Each cavity contains 1000 c.c. of a clear, straw-colored fluid. Otherwise they are negative.

**Pericardial cavity.** Contains 100 c.c. of a clear, straw-colored fluid.

**Heart.** Weight, 430 grms. It is firmly contracted. The edges of the mitral valve are slightly thickened and œdematous. The myocardium is somewhat softer and more moist than normal. The coronary arteries show some sclerosis about their orifices, and a slight sclerotic change along the first cubic centimeter of their course. There appears to be a slight œdema of the myocardium.

**Lungs.** They show quite marked œdema and congestion, the former being most prominent.

**Spleen.** Weight, 130 grams. Surface is smooth. Organ is flabby, cut surface is light red.

**Gastro-intestinal tract.** Normal.

**Pancreas.** Normal.

**Liver.** Weight, 1800 grams. Surface is smooth and on section it is a light reddish brown with pale yellowish mottling.

**Kidneys.** Weight, 620 grams. Capsule nonadherent. Color of surface pale gray, opaque with occasional small deep red foci not over 1 mm., generally less than this, in diameter. The stellate veins injected and prominent. On section the cortex shows a few diffusely scattered red points. The markings are obscure or not visible. The color is pale, with areas of marked opacity. It is more moist than is the normal cortex. The average width of cortex is 1 cm. Over the section, the glomeruli are visible as opaque points. They project above the section, but cannot be felt. Occasionally, they are injected and stand out as red points. The pyramids are of normal size, pale red in color.

**Adrenals.** Are surrounded by fat. Otherwise negative.

**Bladder** negative.

**Genital organs.** There is marked oedema of the scrotum. The tubules of testicles strip easily.

**Aorta.** Shows slight thickening which occurs in yellowish bands running in the direction of the course of vessels.

**Head.** Brain, weight, 1375 grams. Scalp is covered by a good growth of iron gray hair. The tissues of the scalp are enormously swollen with fluid. Calvarium is normal. The pia arachnoid contains a large amount of fluid. There is slight opacity at numerous points, especially along the lines of vessels. Vessels at base show numerous areas of sclerosis, and on section remain wide open. Lateral ventricles contain a few cubic centimeters of clear fluid. Tissues of brain are oedematous.

**Middle ears** normal.

The histological examination of the kidneys showed the glomeruli enlarged, for the most part apparently bloodless, the large size being due to filling of the vessels with cells having vesicular nuclei. The covering epithelium is swollen and shows in places large projecting cells attached to the surface by a process. The intertubular tissue is dilated, and contains foci of hæmorrhage corresponding with the red points mentioned. The epithelium of the tubules is swollen and degenerated, that of the proximal convoluted tubules often containing hyalin globules.

**REMARKS.** Nothing is known as to the history of this case. The renal lesions are typical.

**EXPERIMENTS.** Experimentally hydronephrosis is best produced in the cat by aseptic ligation of a ureter under deep ether anæsthesia, the autopsy being performed three weeks later. The experiment can

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...into the pelvis 0.5 cc. ...  
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...for 3 days of ...  
...nephropathy with edema ...  
...administration by stomach ...  
...are kept in metabolic ...  
...urine made. At the ...  
...and the kidneys are ...  
...usually. Arsenic nephropathy ...  
...quickly, the urine excretes ...  
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be repeated, injecting into the pelvis 0.5 c.c. 24-hour bouillon culture colon bacillus so as to produce pyonephrosis, the autopsy being performed one week later. Various types of acute experimental nephropathy are produced by injecting into rabbits as follows: for tubular nephropathy, 0.05 gram potassium chromate; for vascular nephropathy, 0.001 gram cantharadin in acetic ether; interstitial nephropathy, daily injections for 3 days of 10.0 c.c. 1 : 1000 mercuric chloride solution; acute nephropathy with edema, 0.001 gram uranium nitrate and daily administration by stomach tube of 50 to 100 c.c. water. All the animals are kept in metabolism cages and daily examinations of the urine made. At the termination of 2 or 3 days autopsies are performed and the kidneys and other organs studied grossly and histologically. Arsenic nephropathy (glomerular) has to be studied more quickly, the urine examination and autopsy being made within an hour after the injection of 0.010 gram potassium arsenate.

For the studies in nitrogen metabolism a cat is placed on a meat diet which keeps its weight constant, the non-protein nitrogen and urea nitrogen of the blood being determined by the Folin colorimetric methods on several occasions for purposes of control. The cat is then given 0.002 gram uranium nitrate and on the next day, and alternate days following, the nitrogen determinations made. Daily urine examinations and complete autopsy are to be made. These experiments are followed by a demonstration of the vascular reactions of dogs, the subjects of tubular and vascular nephritis, by the kymographic registration of kidney volume, blood pressure and diuresis.



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## THE PATHOLOGICAL ANATOMY OF THE ALIMENTARY CANAL

From the importance of the alimentary canal both as a surface of the body, thereby in close relation with infection, and from the anatomical and physiological importance of its structure, there have necessarily been numerous inferences in the preceding chapters to its pathology. There are two anatomical conditions, however, which have received no attention. *Ulcer of the stomach* (round ulcer of the stomach, peptic ulcer), differs in a remarkable way from ulcers in other tissues; this is due mainly to the action of the gastric juice. Any necrotic tissue in the stomach is removed not by the ordinary processes of histolysis or organization, or phagocytosis, but by digestion. Small losses of substance in the stomach not extending beneath the mucous membrane, often are associated with superficial hæmorrhages. Both the effused blood and the necrotic mass are digested, giving rise to small superficial, circumscribed losses of substance. Such hæmorrhagic "erosions" seem to have no relation with chronic ulcers.

The *chronic ulcers* most frequent are found in the posterior wall of the pyloric portion of the stomach, or at the junction of this with the cardia. The ulcer is usually round, but may be oval or pear-shaped. The edges do not project. The base and sides are clean, sharp and free from necrotic material. The base is smaller than the surface and the sides often approach the base by a series of step-like processes (terraced ulcer). There is irregularity in this, however, and usually one side of the ulcer, that towards the pylorus by preference, is more perpendicular. The single coats of the stomach often appear in the wall as though artificially dissected. The appearance of the ulcer has been compared with the loss of substance which would be produced by removing a portion of the tissue with a punch. Microscopically, there usually is absence of any marked inflammatory change in the edges or base. There is usually a thin line of granulation tissue on the surface with some induration; the cells on the surface

have the appearance of being necrotic, but this is probably a post mortem change due to the action of the gastric juice. The arteries of the wall of the stomach in the immediate vicinity of the ulcer usually are obliterated either by thrombosis, by enteritis and occasionally by embolus. The process does not, however, involve the arteries at a distance. These ulcers may be single or multiple, and ulcers of a similar character may be found in the duodenum. The etiology of the process is not clear. It does not seem to have any relation with arterio-sclerosis, and is most common at an age prior to that in which arterio-sclerosis is common. The condition is more common in women than in men. The ulcers may produce various results. They may heal with extensive formation of cicatricial tissue and stenosis may be produced by the contraction of this, particularly when the ulcer is near the pylorus. The ulcer may perforate the stomach, in some cases leading to acute peritonitis; in other cases when adhesions have been formed with the surrounding tissue, the ulcer may extend into the pancreas or into the liver, or into the colon. By the action of the gastric juice, necrosis and extensive loss of substance may be produced in neighboring organs when the ulceration extends into these. Extensive and fatal hæmorrhage may result from erosion of blood vessels which have not previously become occluded.

**APPENDICITIS.** This is the most common serious pathological condition in the alimentary canal, and one of the most common of human diseases. In its general histology, the mucous membrane of the appendix resembles that of the large intestine with the important difference that the muscularis mucosa is absent and that there is a very much greater development of lymphoid tissue in the mucosa. The lymph follicles project above the surface and the epithelium dips down between, forming shallow crypts. The whole structure, particularly the proximal end, has much similarity with that of the tonsil.

Acute appendicitis is due to surface infection. In the earliest cases examination shows a small loss of substance of the surface usually in one of the depressions between the lymph follicles. At this point there is an exudation of leucocytes and fibrin which lies partly in the tissue and partly projects into the lumen. Around this there is intense infiltration of leucocytes which often extends through the entire wall. The lumen may be entirely filled by a purulent ex-

update. The process may heal at this stage or extend further, resulting in ulcerative appendicitis. In this condition the purulent infiltration is more extensive, and by softening, ulceration is produced which may lead to perforation. The process may extend into the meso-appendix producing an inflammatory thrombosis of the veins with resulting hæmorrhagic infarction and complete necrosis of the appendix. In the very early cases there may be but little change of the peritoneal surface. Later, the appendix is swollen, red, and the serous surface covered with fibrinous exudate. The uncomplicated acute forms may recover fully, the appendix presenting no evidence of previous disease. Where the ulceration has been extensive, stenosis and complete obliteration may result. Following obliteration, secretion may accumulate in the distal end forming cysts (mucocæle). The etiology of appendicitis is not clear. Foreign bodies, especially intestinal concretions which so frequently are found, probably take no part in its production. Various organisms may be obtained from cultures in the acute cases, but there is no reason to believe that these are other than secondary invaders, and in the most acute cases organisms may be absent.

A CASE OF ACUTE APPENDICITIS WITH PERFORATION AND  
ACUTE PERITONITIS ASSOCIATED WITH COLON  
BACILLUS

**Anatomical Diagnoses.** Acute appendicitis with perforation; General acute peritonitis; Myocarditis (acute); Congestion and œdema of lungs (lower lobes); Acute splenic tumor; Sclerosis of coronary arteries; Sclerosis of mitral valve (aortic cusp); Chronic adhesive pleuritis (right side); Papilloma of shoulder; Double ureter (unilateral.)

White, male, age sixty years. Body well developed and well nourished. There is considerable lividity of lower limbs and of the back. The skin generally is dry and the face has a slight icteroid tint. Situated over the upper portion of the right shoulder, there is a small, pedunculated tumor, 2.5 cm. in diameter. Its surface consists of closely packed, dark-brown papillary processes. This tumor is attached to the adjacent skin by a small pedicle. The abdomen is markedly distended and tympanitic; there is no œdema.

Peritoneal cavity. Fat is well developed and is bright yellow in color. When the peritoneum is cut through, considerable amount of gas escapes

from the peritoneal cavity. The intestines are everywhere deeply injected, and show varying amounts of an acute exudate upon them. This acute exudate consists of small grayish-white plaques or sheets of considerable size, which adhere loosely to the peritoneum covering the intestines. The coils of the small intestine are loosely bound together by a similar exudate. The parietal peritoneum is deeply injected throughout the left side; the anastomosis of the smaller vessels stand out distinctly. The parietal peritoneum shows an acute inflammatory reaction, most marked in the region of the appendix. The upper surface of the liver is coated by a thin layer of exudate. The abdominal cavity contains considerable dark colored, foul smelling fluid; this is most marked in the pelvis. While the peritoneum everywhere shows acute inflammatory reaction, this reaction is most marked in the region of the cæcum. In this latter region, the coils of the intestines are closely adherent and are attached to the overlying parietal peritoneum, walling off an area which contains a considerable amount of dark colored, foul smelling material. The visceral peritoneum and parietal peritoneum enclosed in this area shows a much more marked inflammatory reaction than elsewhere throughout the abdomen. In the former area, that is about the cæcum, the peritoneum shows very marked discoloration. Its blood vessels are deeply injected. The intestines, beginning at the sigmoid and passing upward, show in addition to the acute inflammatory reaction upon their surface no lesions until the cæcum is reached. The cæcum and the appendix present the following appearance. The appendix measures about 8 cm. in length, hangs down free from the lower portion of the cæcum, has a mesentery to its tip, laden with fat. The appendix itself is very markedly discolored, swollen and soft; is easily torn. On the border opposite the mesenteric attachment, and situated 3 cm. from the cæcum, there is a circumscribed, very black area measuring about 6 cm. in diameter. In the centre of this area there is a small opening 3 mm. in diameter, which connects directly with the lumen of the appendix, and through it fecal material escapes upon pressure.

Heart. Normal size. Weight 331 grams. The valves are normal, except a small area in the aortic cusp of the mitral valve, in which locality there is a circumscribed, yellowish area of thickening. On section the myocardium of the left ventricle shows numerous irregularly shaped, very pale, somewhat soft areas, which stand out sharply from the surrounding muscle tissue. These areas vary from pin point to 2 or 3 mm. in diameter, and are generally most numerous in the outer half of the muscular wall, though a few are seen irregularly distributed throughout the ventricular wall. The right coronary artery shows an occasional, small, yellowish, slightly thickened area. The left coronary

artery, about 3 cm. from its beginning, shows upon that portion of the wall which rests against the myocardium, a calcified area about 4 mm. in length. This calcified area involves not more than one-half of the arterial wall. It infringes somewhat on the lumen of the vessel, but does not occlude it. Throughout the remainder of this coronary artery, there is an occasional area of thickening, but no calcified areas.

Lungs. Crepitant throughout. Pleuræ are generally smooth and glistening. No areas of consolidation are noted. The lower surface of the middle lobe on the right side, and the upper surface of the lower lobe on the same side are loosely bound together by a few delicate fibrous adhesions. On section the upper lobes are moist and of a salmon-pink color. The lower lobes are of a light red to a deep red color, and from their cut surfaces a large amount of air-containing blood-stained fluid escapes.

Spleen. This is slightly increased in size. Weight 155 grams. On section the pulp is brownish gray in color and a considerable amount of it adheres to the knife blade.

Liver. Weight 1650 grams. The gall bladder is slightly distended. Its walls and surrounding tissues are deeply stained with bile. The cystic and common bile ducts are patent. The external surface of the liver shows an acute, inflammatory reaction. On section the parenchyma is of a yellow color, and is quite soft; the liver substance just beneath the capsule is very dark red.

Pancreas. Normal. The lesser peritoneal cavity is smooth and glistening. There is no exudate in this area.

Kidneys. Weight 305 grams. They are embedded in a large amount of firm yellow fat. They appear normal in size. On section the cortex is of normal thickness. The glomeruli are distinctly visible as glistening points. The ureter on the left side is normal. Upon the right side the pelvis of the kidney has opening into it two separate ureters, one going to each pole of the kidney. These ureters open into separate pelvises. Throughout 10 cm. of their course this double ureter exists, when the two fuse together leading to a ureter of normal size.

Adrenals normal.

Bladder normal.

Prostate normal.

Aorta. Not opened on account of the undertaker insisting that it be undisturbed.

Cover-slip preparations of the peritoneal exudate showed a variety of organisms, the most numerous being short bacilli conforming morphologically to the colon bacilli which were both free and enclosed in leucocytes.

Microscopic examination of the small foci in the heart showed masses of bacilli similar to those in the peritoneal exudation which are in great part within widely dilated vessels which are occluded by them, and in part in masses in the tissue. About them there is extensive hæmorrhage and the muscle fibres in the vicinity are necrotic, and for the most part disintegrated. Section of the liver with the peritoneal exudation on the surface shows on the surface of the liver a thick meshwork of fibrin filled with polynuclear leucocytes. Above this the exudation contains closely packed leucocytes and but little fibrin. Great numbers of short bacilli are contained in the polynuclear cells and in part are free.

**REMARKS.** The acute peritonitis followed perforation of the gangrenous appendix. The lesions of the heart are due to emboli of bacteria, the embolism taking place shortly before death, and the immense numbers of organisms present is probably to be in part attributed to post mortem growth. The tissue reaction is shown by the necrosis of muscle and the hæmorrhagic exudation. The absence of leucocytes is remarkable. This may be due to several things; to the draining of the leucocytes from the blood by the peritoneal exudation and the inhibition of leucocytic hyperplasia by the toxæmia; to the bacteria having acquired such virulence that the activity of the leucocytes were inhibited. The malformation of the kidney consisting in separate pelves and ureters is one of the most common types of malformation. In this type the double ureter more generally continues into the bladder.

**EXPERIMENTS.** For the performance of the experiments on acute toxic gastritis, cats are to be carefully and deeply anæsthetized with ether, from which they do not recover. Three animals are given respectively carbolic acid, sulphuric acid and nitric acid through a glass stomach tube. The autopsy is performed in 15 minutes and the stomachs studied grossly and histologically. For the production of gastric ulcer, two erosion experiments are performed. In the first, 6 guinea pigs are given about 0.001 gram snake venom and the autopsies performed at the end of 48 hours, typical hæmorrhagic erosions appearing in several of the animals. A dog is anæsthetized and a small amount of agar aseptically injected beneath the mucosa of the stomach. Autopsy at the end of 48 hours shows erosion of the separated mucosa. Of the intestinal lesions the most instructive appears to be the produc-

tion of intussusception. This is done under ether anæsthesia and aseptically, it being found necessary to place one or two stitches so as to maintain the intussusception. Autopsy at the end of 24 hours shows local peritonitis, gangrene and the mode of obstruction.



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371 c













## THE PATHOLOGY OF THE PANCREAS

The pancreas is a large compound gland of entodermal origin, consisting of lobes and lobules, and resembling in its general structure the parotid and submaxillary gland. It contains enclosed within it an epithelial structure, which differs anatomically from that of the acini, has no connection with the secretory ducts, its secretion passing directly into the blood. These structures are known as islands of Langerhans. They are more abundant in the tail and body of the pancreas than in the head, and may also be found in the fat and connective tissue surrounding the pancreas; their secretion is believed to serve an important part in sugar metabolism. The relation of cells and vessels resembles that of the liver, being composed of bands of epithelial cells forming a framework between which run blood vessels in close relation with the cells. The pancreas has no capsule and contains a considerable amount of connective tissue distributed around the ducts, and between the lobules.

The organ has a relatively high resistance to toxins which produces degenerations in other organs. The parenchymatous degenerations, so common in the infectious diseases, either are not present or in but slight degree. The pancreas is also resistant to infections, particularly those of hæmatogenous origin. In cases of hæmatogenous tuberculosis, miliary tubercles rarely are found in its tissue. In congenital syphilis large numbers of treponemata may be found in the gland with but few lesions associated with their presence; the lesions of acquired syphilis are rare also. Metastatic abscesses are infrequent and the same is true of primary and secondary tumors. In these relations the pathology of the pancreas is similar to that of the parotid and submaxillary glands, and what has been said of the pancreas holds true for these glands also. Injurious substances affecting the gland usually reach it by means of the secretory ducts and the pathology of the pancreas is intimately related to its ducts. It possesses two secretory ducts; the chief of these is the

duct of Wirsung which begins at the tail, runs through the middle of the pancreas, bending downward as it passes through the head. Branches from other portions of the pancreas enter into this duct at right angles. It descends in front of the common bile duct and empties in common with the latter into the duodenum at the papilla of Vater. It often terminates in the floor of the papilla, thus giving a common opening for both pancreatic and bile ducts. The tributary ducts of the head are larger than the others. A large branch of the pancreatic duct, the duct of Santorini which is the chief duct of the head of the pancreas, may empty into the duct of Wirsung as this passes through the head, but in about one-half of the cases opens independently into the duodenum. Even when so terminating, it still retains its connection with the duct of Wirsung and the entire secretion of the gland may be discharged through it. The pancreatic secretion plays an important part in digestion by means of its three enzymes, trypsin, diastase and lipase. It is generally believed that the internal secretion produced by the islands of Langerhans contains the enzyme necessary for the hydrolysis or oxidation of sugar, and in the absence of this secretion sugar accumulates in the blood and is excreted by the kidneys, *glycosuria*. Regeneration of the pancreas takes place to a limited extent only.

**DEGENERATION AND NECROSIS.** Small foci of necrotic cells not infrequently are found in the pancreas. These vary in size from single necrotic cells to areas a millimeter or more in diameter and usually occupy no fixed location within the lobule. In association with the necrosis, there is infiltration with polynuclear leucocytes. Small foci of atrophy and increase of connective tissue are found, which represent the results of such necroses.

Atrophy and sclerosis affecting the entire organ and leading to diminution in size and induration also may occur. The surface is uneven and irregular. This change may take place in the pancreas without involving the islands of Langerhans in the process, or these may also be affected. The pancreas may also be affected together with the liver in hæmochromatosis. In this condition there is atrophy and sclerosis of the gland associated with the presence of large amounts of iron-containing pigment in the interstitial tissue. When the Islands of Langerhans are involved, *diabetes* may be associated with the pigmentation, the condition being known clinically as *bronze diabetes*.

**INFLAMMATIONS.** Three types of acute inflammation of the pancreas are described. In *acute hæmorrhagic pancreatitis* the pancreas is enlarged and infiltrated with blood. The condition may appear in foci, or the entire organ may present the appearance of hæmorrhagic infarction. The blood may pass from the pancreas into the surrounding tissue and into the lesser peritoneal cavity. Microscopically, the gland shows, in addition to the hæmorrhage, areas of necrosis of the parenchyma and cellular and fibrinous exudation. The hæmorrhagic condition may be associated with *gangrenous pancreatitis* in which the gland is enlarged, soft and friable, the color varying from gray to black. Complete sequestration of the necrotic tissue may take place and the pancreas be represented by a necrotic, soft gray mass lying free in the lesser peritoneal cavity. *Suppuration*, in the form either of circumscribed abscesses or as a purulent infiltration of the tissue, is comparatively rare, but may be combined with the hæmorrhagic form. The origin of acute pancreatitis has been cleared up by experimental study. It has been found that the injection of a large number of substances into the pancreatic duct will produce the condition. The injection of bile into the duct produces extensive injury and in man the disease often follows the occlusion of the papilla by a gall stone which allows the bile from the common bile duct to enter the pancreatic duct; this takes place only when the ducts are united near the opening. Such conditions in the pancreas frequently are accompanied by fat necrosis. This is due to an escape of the pancreatic fluid into the tissue, leading to the production of foci of necrosis in the interstitial fat of the gland, or in the surrounding fat or in the fat of the peritoneal cavity. (See necrosis, page 43.)

Calculi may form in the ducts, producing occlusion followed by cyst formation. There is usually considerable atrophy of the tissue associated with this condition.

#### ACUTE GANGRENOUS PANCREATITIS

**Anatomical Diagnoses.** Acute gangrenous pancreatitis; Acute peritonitis; Fat necroses; Chronic cholecystitis; Chronic cholangitis; Cholecystotomy; Chronic localized peritonitis; Jaundice; Ulcer of lower lip; Multiple hæmorrhages in lungs and skin; Chronic perisplenitis; Concretion in duct of Wirsung; Subpial œdema; Cyst of choroid.

White, male, age twenty-seven years. Body well developed, fairly well nourished. Rigor mortis and lividity present. Skin is yellow. In lumbar region and over the left knee are areas showing discrete, petechial and macular purpuric spots. On right side of lower lip is an ulcerated area 1.5 cm. in diameter. Slight oedema below the lower eyelids. In right upper quadrant of abdomen opposite attachment of ninth rib and extending vertically downward for 6 cm. is an operation wound the lower half of which is healed; the upper half is open and discharges a brownish colored thick material. The edges of the wound pale reddish brown. Two small sloughing ulcers on either side of the wound at site of skin sutures. Sclera and conjunctivæ markedly jaundiced.

Peritoneal cavity. Subcutaneous fat moderate in amount. Irregularly distributed over the peritoneum; covering the great omentum and the cæcum, are numerous small discrete irregularly shaped grayish-white to yellowish-white, soft, rather granular areas. They average from 3 to 5 mm. in diameter. Some of them over the cæcum have a distinct greenish discoloration. The transverse colon, the lesser omentum and stomach bulge forward and beneath them distinct fluctuation is present. This fluctuation is produced by the contents of an abscess cavity which is situated in the lesser peritoneal cavity. This cavity contains 1500 c.c. of a brownish, gruel-like fluid throughout which small gray-white bits of tissue are seen. Its walls are shaggy and lined with a gray, necrotic material. The foramen of Winslow is obliterated by dense adhesions. This cavity continues along the lower surface of the left lobe of the liver to a slight extent under the right lobe, and downward behind the peritoneum along the course of the descending colon as far as the cæcum. This cavity communicates with the gall bladder by an opening in this and through the gall bladder with the opening in the abdominal wall.

Pleural cavities normal.

Pericardial cavity normal.

Heart. Weight 280 grams. Myocardium normal. Cusps of aortic valve slightly thickened at bases. There are a few yellowish-white, thickened areas in the aortic segment of the mitral valve. Coronaries normal.

Lungs. Both are crepitant throughout. On section a few small, dark reddish areas are irregularly distributed.

Spleen. Weight 132 grams. Soft. Covered with dense fibrous adhesions. Near the hilus is a dark green soft area. Spleen generally deep red. Trabeculæ prominent.

Gastro-intestinal tract. Œsophagus negative. Stomach contracted and empty. Rugæ prominent. No gastric ulceration. Walls rather soft, greenish gray and covered with fibrous tags. Duodenum

deep greenish gray. Biliary and pancreatic ducts are patent, but small. Intestines normal, except for adhesions about the cæcum and transverse colon. Intestinal contents are grayish white and contain small, "chalky-like" flakes scattered throughout. Examination shows large amount of fat.

**Pancreas.** Practically the whole of the pancreas is represented by a grey or white to deep red, soft, friable, soapy feeling material. A small portion of the head remains as a deep red rather firm tissue. The duct of Wirsung about 1 cm. from its opening into duodenum is occluded by a gray, firm mass, 3 mm. in diameter.

**Liver.** Slightly increased in size, deeply bile stained, lobules distinct. Portal systems dilated. Gall bladder is continuous with the fistulous opening in the abdomen. Cystic duct is somewhat narrowed; it is impossible to pass a probe through it in either direction. The hepatic duct patent, as is also the common bile duct, though narrowed just prior to the opening into the duodenum. No gall stones.

**Kidneys.** Weight 350 grams. Capsules not adherent and leave a smooth surface on stripping. On section the cut edges of the kidney slightly everted. Cortex 0.75 to 1 cm. in thickness. Deep red. Glomeruli indistinct. Pyramids, pelvis and ureters normal.

**Bladder.** Contains about 150 c.c. of clear, straw-colored urine. Genital organs normal.

**Aorta** rather pale.

**Head.** Brain, weight, 1370 grams. Scalp covered with short black hair. Scalp and calvarium normal. There is slight œdema of the pia and a slightly increased amount of cerebrospinal fluid at the base of the brain. The fluid in the lateral ventricles is normal in amount and bile stained. There is a small cyst in the choroid plexus of the left lateral ventricle. The cerebrum, cerebellum, pons, medulla and basal nuclei, on serial section, are normal.

**Middle ears** normal.

**REMARKS.** The hæmorrhages in the skin and elsewhere are related to the jaundice. The bile salts favor hæmorrhage by retarding the coagulation time of the blood and probably also by producing endothelial necroses. The acute gangrenous pancreatitis is interesting in association with the calculus in the duct of Wirsung. Had there been a single opening through which the two ducts discharge, and had the calculus occluded this, the acute pancreatitis would be easy of explanation by the entry of bile into the pancreatic duct. In this case the obstruction of the duct by the calculus facilitated the infection of the contents producing acute

inflammation. The fat necroses are due to escape of pancreatic secretion into the tissue and the white fatty contents of the intestine to the absence of the action of the pancreatic secretion.

**EXPERIMENTS.** Acute hæmorrhagic and necrotic pancreatitis is produced by injecting into the pancreatic duct of a dog (ether anæsthesia), either through the papilla or directly into the duct, about 3 c.c. dog's bile (same animal — obtained by gall bladder puncture). At the end of 24 hours most marked pancreatitis and extensive fat necrosis appear. Most important in connection with the pancreas is diabetes and at this time experiments in glycosuria are best made. Pancreatic glycosuria is produced by completely extirpating the dog's pancreas, aseptically and under ether anæsthesia. The animal is observed in a metabolism cage. For other forms of glycosuria the rabbit is used as follows: for renal glycosuria, the hypodermic injection of 0.25 gram phlorrhizin dissolved in 5.0 c.c. warm water; for asphyxial glycosuria, hypodermic injection 2-3 c.c. 4 per cent morphine sulphate solution; adrenalin glycosuria, hypodermic injection 2.0 c.c. 1:1000 adrenalin solution. The animals are observed closely in metabolism cages and advantage is taken of the morphinized animal to make pneumographic tracings of Cheyne-Stokes respiration. The so-called puncture glycosuria is produced as follows: Under ether anæsthesia expose the occipital protuberance of a rabbit's skull, trephine just posteriorly and push in through the cerebellum a special puncture knife. Hold the instrument so that it will bisect the line joining the external opening of the two ears and send it in until it is felt to have met the basilar bone. Place in metabolism cage and examine the urine in 2 hours. At death perform autopsy and verify position of puncture.

377 a





**377 c**



## THE PATHOLOGY OF THE LIVER

THE INFECTIONS of the liver present no peculiarities except those due to anatomical structure and which determine the mode of entry of infecting organisms and their extension. The abundant blood supply of the liver and the slowness of circulation favor the entry of organisms from the blood and the comparative infrequency of infection argues a relatively high degree of resistance.

DEGENERATION AND REGENERATION. The key to most of the anatomical lesions of the liver is given by a consideration of the relations between degeneration and regeneration and repair. Both the less severe forms of degeneration and necrosis are common in the liver. The liver cells are extremely sensitive to the action of toxins, bacterial or other, which are formed in the course of infections and to the toxic action of certain drugs, such as phosphorous and chloroform. In most cases the cells around the centres of lobules are more easily affected and the necroses are more usually central. In other cases the necrosis may be confined to the mid-zone of the lobule and rarely to the periphery. In phosphorous poisoning the necrosis is irregular in its distribution and in yellow fever single cells, chiefly in the periphery of the lobule, are affected. Extensive necrosis follows fracture of the liver due to trauma, the fracture shutting off areas from circulation. The process of regeneration and repair has already been considered (see page 128).

ACUTE YELLOW ATROPHY. The most extreme degrees of degeneration and necrosis are found in *acute yellow atrophy* of the liver. In the most acute cases of this disease, the liver is small; in the adult the weight may be reduced to 600 grams, lax in consistency, the edges sharp, the color yellow or yellow brown. The laxity of tissue is so great that the organ flattens when laid on a surface. Microscopically, the picture is that of intense degeneration with much fat in the cells, necrosis and histolysis. In places the liver cells are represented by a granular mass in which neither cell outlines nor nuclei can be found. Large areas of the liver are so affected, but in places comparatively well preserved lobules may be found. The condition where the acute degeneration is most marked is such

as might be produced by washing out most of the liver cells leaving the collapsed framework. In the less acute cases the atrophy is marked, but the loss of consistency not so extreme and sections of the liver shows an alternation of slightly elevated irregularly distributed yellow areas in a tough, lax, red or red-brown tissue. The yellow areas have irregular contours and may be several centimeters in diameter. Microscopic examination at this stage shows in the red tissue a network of fine canals lined with low epithelium. A lumen sometimes is visible. Between these structures is a tissue filled with large cells of endothelial character and abundant capillaries. In places areas of injected capillaries are found which in arrangement simulate those of the lobule. In the yellow areas liver tissue variously altered is found. At the edges of the yellow areas, degenerated and necrotic cells are found and there is everywhere a varying degree of degeneration. In places the degenerated areas show the normal architecture of the liver, in others there is a wide departure from this, shown in the increased size and irregular structure of the lobules. The liver cells are large, the bile capillaries dilated and often filled with bile casts. Fragments of such casts may be seen within endothelial cells in the sinuses and the casts themselves may project from the bile capillaries into the sinuses. In the red areas the interlobular spaces are represented by the bile ducts which are but little altered; the interlobular vessels are not so apparent. Cases have been described of apparent recovery in which the liver returns to a normal color and consists of irregular masses of liver tissue in which the lobules are large and irregular in structure, the masses surrounded by and infiltrated with dense connective tissue containing the duct-like structures already described. The disease ordinarily runs an acute course, with jaundice and delirium, death taking place within two or three weeks. The ætiology is obscure; the condition often accompanies or follows severe infections, may follow pregnancy, prolonged chloroform narcosis, or appear without any recognized antecedent condition. The condition is obviously one of degeneration and histolysis of the liver parenchyma followed by regeneration, most of the liver tissue in the subacute and chronic cases being regenerated. There has been considerable dispute as to the character of the duct-like structures in the atrophic tissue. They form an anastomosing network in this, which communicates with the remaining inter-

lobular bile ducts, and they are due to regenerative outgrowth from the original bile ducts. Structures very similar in character may be produced by atrophy of the liver cell columns, but in acute yellow atrophy there is necrosis and histolysis of the liver tissue and not a simple atrophy. The capacity of the bile ducts epithelium for regenerative proliferation is shown in the regeneration of liver following traumatic destruction (see page 128).

**CIRRHOSIS OF THE LIVER.** (*Chronic interstitial hepatitis.*) The essential conditions in cirrhosis are degeneration and destruction of tissue followed by connective tissue increase and new formation of parenchyma. Instead of being acute, as in yellow atrophy, the process is extremely chronic extending over years, and there is great variety in the anatomical picture, due to the period of disease, rapidity of progress, character of degeneration and extent of repair. The most common and most characteristic form of the disease is *atrophic cirrhosis*. In this the liver is reduced in size, weights under 1000 grams in adults are not uncommon, it is firm and the surface irregular and nodular, hobnail liver. The irregular and nodular surface is due to projections of the less altered parenchyma separated by cicatricial depressions. The color varies; it may be darker than normal, yellow or pale from an increased fat content, or green or green yellow from retained bile pigment. On section it is dense, often of almost cartilaginous consistency, and the cut surface shows nodules separated by more transparent bands of connective tissue. Microscopically, the picture corresponds with the macroscopic appearance. The connective tissue bands separate the areas of parenchyma. Single (monolobular cirrhosis) or several (multilobular cirrhosis) lobules may be so enclosed, and the connective tissue often extends in finer bands into the lobule. The bands form around the periphery of the lobules, there being no increase of tissue around the central vein (cardiac cirrhosis, see page 90). There is always infiltration of the connective tissue with lymphoid cells which often are aggregated in clusters. The connective tissue is fibrillar and contains a large amount of elastic tissue. The duct-like structures, previously described, are almost always present. At the edge of the liver cells they are continuous with evidently atrophic cells, and these again are continuous with normal cells and the formation of duct-like structures by atrophy of liver cells in the usual mode. The arteries of the liver rarely show lesions even in cases of arterio-

sclerosis elsewhere; the visible portal veins are usually dilated. Small masses of liver cells without lobular arrangement may be enclosed in the connective tissue. The liver cells in form and in arrangement show no considerable departure from normal; frequently areas evidently of new formation, are found in which the lobules are much larger than normal and the hepatic vein eccentrically placed. The newly formed cells are often larger, more distinct and the nuclei contain more chromatin than the normal. In other cases various evidences of degeneration, and even extensive cell necrosis, is seen. A peculiar form of degeneration characterized by amitotic nuclear division, the single cell containing a number of nuclei with but small chromatin content, is not infrequent. The presence or absence of cell degeneration is due to the examination being made in periods of extension or quiescence of the disease. The disease is essentially one of adults; it is due to the long continued action of toxic agents of little intensity of action, and frequently is associated with alcoholism. It is not so infrequent in children as generally is supposed. Arterio-sclerosis, which plays so important a part in the very similar condition of chronic diffuse nephropathy, seems to be in so far as local arterio-sclerosis is concerned, of no ætiological significance in atrophic cirrhosis.

The underlying conditions in *hypertrophic cirrhosis* (Hanot's cirrhosis) are very similar to those of the atrophic, but the lesions differ both in their macroscopic and microscopic aspects. In this condition the liver is greatly enlarged, the weight in adults frequently being 3000 grams, the surface either smooth or finely granular, the color pale or yellow. The consistency is greatly increased and the surface homogeneous on section. Microscopically, there usually is well-marked degeneration and a diffuse formation of connective tissue not only around the periphery of the lobules, but extending into them and around individual cells. In the connective tissue there are large numbers of ducts and marked lymphoid cell infiltration. There is degeneration, necrosis and destruction of liver cells. The condition clinically is always more acute than is the atrophic form. It is a comparatively rare disease. Hanot's cirrhosis has been described by French authors as probably due to an indefinite but specific infection, and there is little doubt that infectious processes play an important rôle in the production of all forms of cirrhosis.

Various other types of cirrhosis are distinguished, as biliary, syphilitic, etc., and which are due to different modes of production of the primary injury.

#### A CASE OF ACUTE YELLOW ATROPHY OF THE LIVER

-- Anatomical Diagnoses. Acute yellow atrophy of the liver; Hypostatic congestion of the lungs; Acute congestion of the spleen; Localized congestion of small intestines; General bile pigmentation of the tissues.

White, male, age forty years. Admitted to hospital January twenty-nine, with the following history: For three weeks had not been feeling well. One week before admission quit work on account of general weakness and because he was becoming yellow. Three days before he came to hospital became delirious. On admission to hospital was wildly delirious requiring restraint. Pulse was not rapid. Passed urine and feces involuntarily. Physical examination was negative except for the jaundice and for a marked decrease in hepatic dullness which was reduced in the right nipple line to an area not more than one inch in width. Diagnosis of acute yellow atrophy of liver. During the next twenty-four hours the patient became quieter, but was not able mentally to give any account of himself. He died before midnight January 31st.

Body powerfully built, fairly well nourished, not fat. The entire surface of the body and conjunctivæ intensely jaundiced. The jaundice is a pale yellow color except along the inner surfaces of the thighs and about the pubes, where the yellow has deepened. The dependent parts show post-mortem lividity, with a combination of purple-red and yellow areas. Scattered over the thorax there are small red *nævi* from 2 to 5 mm. in diameter, from ten to fifteen in number, and some of these are capped by a small superficial crust. There are no areas of hæmorrhage in the skin. Rigor mortis marked.

The abdomen is moderately distended, tympanitic. Percussion of the right thorax shows anteriorly pulmonary resonance, passing directly into the abdominal tympany without any intervening area of hepatic flatness. On opening the abdomen the intestines are moderately distended; liver or spleen not visible. The peritoneum is everywhere glistening and smooth. There is no increase in peritoneal fluid. The small intestine is moderately distended with gas, the large intestine, except the cæcum, is rather collapsed. The lower border of the liver is well above the costal margin and has to be pulled down in order to be visible. The lower border of the spleen is slightly above the costal

margin. The thorax and both pleural cavities are free from fluid and adhesions.

The lungs are rather voluminous, deeply pigmented with carbon in the posterior portions; and the lower lobes are soggy and firmer than the tissue elsewhere. The lung, however, crepitates everywhere. Cut surface of the lungs is moist. A moderate amount of mucous or mucopus exudes from the small bronchi and from the alveoli, and a frothy serum in moderate amount runs out. There are no distinct areas of consolidation. The entire cut surfaces are a fairly uniform dark reddish color.

The peribronchial lymph nodes are very slightly enlarged, show carbon pigmentation, but no other abnormality. The bronchi are congested and contain a moderate amount of mucous and mucopus. The pericardium contains about 75 c.c. of clear fluid of a dark yellow color. The pericardium is everywhere smooth and glistening. The heart is normal in size and shape. Endocardium normal; valves normal; coronary arteries normal. The endothelial surfaces of the aorta and pulmonary artery are stained yellow by the bile pigmentation, as is also the fat and areolar tissue about the heart.

Liver. Weight 1000 grams. The surface of right lobe shows along the upper surface two rather distinct rounded elevations from 4 to 6 cm. in diameter, which project somewhat above the surrounding surface, are dome-shaped, the contour not particularly smooth, there being small elevations upon the general rounded surface. The lower half of the right lobe shows a somewhat elevated surface presenting the same slight irregularity. On the inferior surface this same arrangement appears, and on the inferior surface of the extreme lower portion there is a cleft in the surface of the liver 4 cm. long and 3 cm. deep. As seen through the capsule, which is in no place thickened, these more elevated areas are yellow or yellow red in color. After exposure to the air the yellow becomes green; corresponding to the smaller elevations on the surface of the larger elevations, there is a slight mottling, the more elevated areas being more yellow and the depressed areas being more red. Between these more distinct elevations the surface of the liver is in general red and slightly wrinkled. The elevated areas are firm, the larger one distinctly firmer than normal. The more depressed portions, which are red, are distinctly flabby. The cut surface of the liver shows two very distinct appearances. There are considerable areas which are red in color, showing over their surface a fine distribution of red-gray tracery of somewhat the appearance that is given by the liver of chronic passive congestion without the central depressions. The other parts of the liver are bright yellow, turning green on exposure to the air, and these areas



seem to be made up of liver lobules distinctly larger than those suggested by the tracery in the red. It would seem as if there were a small central vein and about it liver tissue from 1 to 1.5 mm. in thickness, such a group forming what is taken to be a liver lobule somewhat larger than normal. The amount of these two different kinds of tissue varies on a given cross section. In portions of the liver they are equal, in other parts red predominates, in still others yellow. The vessels seen on the section appear to be normal. This description applies entirely to the right lobe of the liver. The left lobe of the liver is represented by a thin, flabby red tissue, with slightly wrinkled surface, showing at two places slightly elevated yellow areas, one being 2 cm. in diameter, the other 1.5 cm. The tissue in the left lobe resembles on section the red parts of the right lobe, and is distinctly tougher than normal.

The spleen weighs 205 grams, is somewhat softer than normal. Cut surface is of uniform dark red color with malpighian bodies just visible; pulp scrapes away slightly more easily than normal.

Gastro-intestinal tract. Esophagus is normal. The stomach is considerably dilated and filled with a brown-gray fluid containing a considerable amount of mucous. Mucous membrane of the stomach is normal except for a considerable amount of adherent mucous. Pyloric ring is contracted, but there is no evident hypertrophy and no actual obstruction. The small intestine is normal, except for a distance of about eighteen inches, beginning at a point about thirty-six inches above the ileo-cæcal valve, where it is very much congested. The mucous membrane is dark red in color. In places this congestion is uniform in its distribution, in other places it affects mainly the tops of the folds of the mucous membrane. There is no evidence of ulceration or erosion in this region and, except for this area, the small intestine shows no other abnormality. Then in the lower portion there are scattered solitary follicles showing a distinct zone of hyperæmia about them. The large intestine and the appendix are normal. The pancreas is large, fairly firm and shows no abnormality on section. The biliary ducts and pancreatic ducts are normal. The gall bladder is filled with thick, dark bile, but there are no concretions and its mucous membrane appears normal.

The kidneys are somewhat larger than normal, appear slightly swollen and are of a red-purple color. The capsule strips quite easily from the smooth surface. The cut surface shows a rather dark tissue, in general color purple with slightly evident yellowish tint. There is nothing abnormal in the appearance of the cortex or the pyramids. The adrenals are normal in appearance. The bladder, prostate and testes are normal. The aorta is normal. The thyroid is normal. Some of the lymph nodes

of the abdomen are moderately enlarged and show distinct bile pigmentation.

Microscopical examination of the liver. Sections of liver stained in methylene blue and eosin show two distinct areas; in one of these areas, which corresponds with the red areas, the liver cells have disappeared leaving foci of injection and hæmorrhage around the central veins and containing great numbers of epithelial strands or ducts around the portal vessels; in the other, which corresponds with the yellow areas, the liver tissue is of somewhat atypical character with increase of connective tissue. More detailed examination shows in the red areas a general collapse of the tissue with diminution of the distance between hepatic and portal vessels. There is blood both free and in spaces which corresponds with liver capillaries between which is thick connective tissue containing numbers of cells. There is great thickening of the tissue about the central veins, and the congestion and hæmorrhage are most marked about the central veins. In the portal territories the artery, vein and bile duct appear as normally, and about them is the irregular network of epithelial tubules. The strands of these vary in diameter from 10 to 30  $\mu$ . The outline of the individual cells composing them cannot be distinguished; the cells appear as a syncytium containing a large number of nuclei which have epithelial characteristics. Here and there definite lumina can be distinguished in the structures. This network communicates with the definite bile ducts in the portal spaces but the communications are rare. The bile duct gives off a lateral which at first has the characteristics of a bile duct, but quickly takes the character of the network and forms part of this. The network is closer near the portal spaces. Neither nuclear figures nor nuclei indicating direct division are found in the network. Pointed processes not unlike forming vessels are given off from it. In places there is a change in the character of the cells composing it. The cells become larger and fewer in number, the nuclei larger, their cytoplasm acidophilic and there are transitions between such cells and definite liver cells. Where this change is taking place, there are numbers of polynuclear and large endothelial cells in the tissue. Masses of liver cells are connected with these epithelial structures. The cells show no evidences of degeneration, they are very granular and have large nuclei rich in chromatin. The capillary bile ducts between the cells are very evident, are dilated and often contain bile casts. The interpretation is total destruction of liver tissue and a new formation by development of the epithelium of the ducts which represent an outgrowth from the bile ducts into liver cells.

The yellow areas show islands of liver tissue separated by bands of connective tissue. These islands vary in size, none of them larger than

1 mm. The lines of connective tissue have an indefinite arrangement following both the hepatic and portal spaces. The liver tissue around the central veins has greatly dilated bile capillaries filled with casts which occasionally project from the liver cell columns into the capillaries. Such casts never are found in the vicinity of the portal spaces. About the central veins also, cells in various stages of degeneration are found. Some of these are represented by vacuolated masses, others by irregular masses of cytoplasm filled with bile pigment, and in their vicinity there are numbers of phagocytic endothelial cells. These degenerated cells in part occur singly; in part they are in masses which are continuous with the more nearly normal cells. It is difficult to determine whether these degenerated cells should be regarded as old liver cells or as new cells which have undergone degeneration. The masses of liver here are atypical. The capillaries are in places short, in places of abnormal length, and the trabeculae of the liver cells in places conform to the normal type and in places they are much broader making four or five rows of cells. About the portal spaces there are numbers of bile ducts both normal and atypical. The cells are intensely granular and rather smaller than normal cells. The capillaries in the areas contain but little blood. The interpretation is that the liver tissue in the yellow areas is newly formed.

**REMARKS.** This is a typical case of acute yellow atrophy of the liver. The duration cannot be determined with definiteness, but the acute symptoms are of but nine days' duration. It is almost impossible to avoid the conclusion that practically the entire liver was destroyed and that the yellow areas represent regenerated tissue.

It is not impossible that in these areas the destruction was slower and that much of the regeneration was by means of hyperplasia of the liver cells. The jaundice is easily understood. Bile was formed in the cells, but the tissue was so altered that it could not easily enter the bile ducts; it accumulated and became thickened into casts which passed from the bile capillaries directly into the blood.

#### A CASE OF CIRRHOSIS OF LIVER

**Anatomical Diagnoses.** Cirrhosis of liver; General arterio-sclerosis; Chronic peritonitis (adhesive); Chronic pleurisy (adhesive); Heart hypertrophy; Chronic perisplenitis (adhesive); Ascites; Chronic passive congestion of spleen; Chronic passive congestion of kidneys; Chronic diffuse nephropathy; Oedema of lungs; Oedema; Jaundice.

White, male, age sixty-one years. Body well developed and fairly well nourished. Post-mortem lividity is marked over face and dependent portions of body. Rigor mortis is present. There is œdema of ankles and of scrotum. Scleræ have a distinct yellow tinge. The abdomen makes a rather abrupt rise just below the ribs, reaching to a height of 30 cm. above the table. The umbilicus protrudes and the contents of the abdomen are fluctuant. The skin all over the body has a distinct yellow-green color.

Peritoneal cavity. Contains about 11,000 c.c. of fluid (9500 c.c. measured, and remainder estimated). This fluid has a distinct red tinge and floating in it are stringy masses of fibrin, some of which are very short and others two or more centimetres in length. Visceral peritoneum is smooth and glistening. Appendix is 12 cm. long and has a mesentery which reaches to the tip. It is curled about the cæcum so that the tip lies to the inside and in front of the cæcal wall. The mesentery contains an enormous amount of fat. The lymph nodes are not enlarged. Diaphragm, left sixth rib, right fifth rib.

Pleural cavities. On the left side the pleura is smooth glistening and deep red in color. On the right the pleura is very adherent by old, dense adhesions.

Pericardial cavity. It is rather large and contains a slightly larger amount of fluid than usual. The smaller vessels stand out very clearly on the parietal layer. There are several white thickened areas on the visceral layer.

Heart. Weight 410 grams. The coronary arteries are conspicuous. On section their walls are thick and very stiff. The intima is yellow and in some areas quite hard. The heart muscle is deep red in color and firm to the touch. Valves are slightly and uniformly thickened and yellow in color. The aortic ring has bulging from its margin into the lumen several large projections which are hard and wart-like. They are gritty and sound like bone when tapped with the scalpel handle.

Lungs. Left: has a very deep red color. Crepitation in somewhat decreased. On section it contains a great deal of dark red fluid which can be expressed as red foam. The bronchi and bronchial glands are negative.

Right: external surface presents a very shaggy appearance. On section it is similar to the left save that there seems to be a little less fluid and the lung has a very distinct brown-red color.

Spleen. Weight 310 grams, of firm consistency and white color. Organ is gray in color. On section the capsule and trabeculæ are thickened. The follicles are not visible. Capsule is grayish brown in color.

**Gastro-intestinal tract.** The colon is dilated and contains a gray-green fluid. The walls are very dark red. There is no ulceration.

**Pancreas.** It is rather large and is yellow from the great amount of fat in which it is embedded.

**Liver** weighs 1900 grams. It is extremely firm, preserves its shape when laid on the table, shows somewhat rounded edges and a moderately thickened, opaque capsule. The surface shows projecting yellowish-brown, relatively soft nodules, averaging from 3 to 5 mm. in diameter and separated by firm gray depressed bands of connective tissue. The organ cuts with leathery resistance and shows a generally retracted cut surface, in which lobular markings are not preserved, but showing a slightly projecting yellowish-brown parenchyma and a retracted network of gray scar tissue. Gall bladder and ducts are normal.

**Kidneys.** Weight 400 grams. Several small cysts can be seen on the surface and one or two depressions are seen near the poles. The capsules strip with difficulty leaving the surface slightly granular. The stellate veins are prominent. The cortex measures from 6 to 8 mm. and in places is distinctly yellow. The glomeruli can be seen as glistening dots. The pyramids are closely outlined.

Adrenals negative.

Bladder negative.

Genital organs negative.

**Aorta.** The arch is stiffened by a deposit of yellowish, gritty material and in one area, 1 cm. in diameter, there is a shallow excavation which has a jagged border of very hard material. The floor of this patch is roughened and yellow green in color. The descending portion of the thoracic aorta is thickened and there are long, raised, yellow patches beneath the intima. The abdominal aorta has a greater number of patches than the thoracic and the rings about the intercostal branches contain calcareous material.

**REMARKS.** The liver is larger than is usual in this type of cirrhosis, but the size may vary greatly. The enormous ascites is due to the long standing obstruction to the portal circulation. The enlarged and fibrous spleen is characteristic. The heart hypertrophy is due both to the chronic diffuse nephropathy and to the calcification of the aortic valves which slightly obstructed the outlet. Such valvular changes, as here described, are due to the extension to the valves of the sclerosis of the aorta and not to a preceding acute endocarditis.

**EXPERIMENTS.** Experimental focal necrosis of the liver has been studied in connection with the experiments on blood destruction (see p. 69) and those on necrosis (see p. 43). A similar condition can be produced by injecting 0.5 c.c. ether into the posterior auricular vein of a rabbit or 2.0 c.c. ether into the jugular vein of a cat. Histologic sections are to be made 24 hours later. Of interest is the jaundice produced by the ligature of the common bile duct of the dog, studying the general jaundice, pallid stools and the pigmentation of the urine. Experimental cirrhosis is best produced by ligating the common duct of a rabbit and performing the autopsy at the end of 4 weeks. Striking gross and histological pictures are obtained.







389 c



## THE PATHOLOGY OF THE LUNGS

Infection plays the dominant rôle in the production of lesions in the lungs. Certain of the infections and other lesions have already been considered (see particularly Lobar Pneumonia, page 225). While many of the lung infections are primary, yet when the infections are considered as a whole, probably the most are secondary to infection elsewhere, which may supply the infectious agents, produce conditions which facilitate their entry into the tissue, or lower the general resistance. In most of the secondary infections, the three conditions act together.

**BRONCHO-PNEUMONIA.** The most important of the secondary infections is *broncho-pneumonia* (catarrhal pneumonia, lobular pneumonia). The disease is much more common in children than in adults, so common that it is found in more than half of all autopsies of children under two years of age. The lesions consist in the presence of foci of inflammation in the lung, in relation to the bronchi, representing the results of the action of injurious substances which enter the lung by means of the bronchi. The foci may be few in number, or they may be very numerous and evenly distributed through the tissue. The lower lobes and the posterior portions of the lungs are more frequently affected than are the upper lobes and the anterior portions. The exudate fills the alveoli in the affected areas; these may be felt as hard shot-like areas and appear on section as slightly projecting areas which usually are somewhat paler than the general parenchyma. The character of the exudation varies, to some extent, with the character of the injurious agent, and may be serous, purulent, hæmorrhagic or fibrinous, the last being as definite as in lobar pneumonia. With the exudation there often are found in the alveoli numbers of the large cells of endothelial character, the presence of which has given rise to the synonym catarrhal pneumonia, a term happily falling into obsolescence. Large areas of solidification, two or more centimeters in diameter, may be produced by confluence of small foci, or without confluence these may be so closely set as to give the impression of extensive solidification; portions cut from such areas, however, do not sink

in water. Entire lobules of the lung may be affected, this giving rise to the synonym "lobular pneumonia." By "lobule" in this connection is understood not the histological lobule into which the terminal bronchus enters, but the anatomical lobule which contains in the neighborhood of one hundred such terminal units and is indicated on the pleural surface by the field separated by the lines of the pleural lymphatics. The histogenesis of the process can be studied best in areas from an affected part, which present no lesions to the naked eye. In such tissues foci may be seen in which the exudation is confined to the atrium and from this primary point of infection the process extends. Extension to neighboring lobules through the alveolar walls does not take place to any considerable degree, the extension being rather by the continuous involvement of other terminal bronchi and of their related alveoli. The pleura may be affected, but not so frequently, nor to the same degree, as in lobar pneumonia.

There is no single ætiological agent. The streptococci, the pneumococci, the staphylococci are found in almost equal frequency, and the same organism may, in different cases, produce all the varied forms of exudation.

**ASPIRATION PNEUMONIA.** Another form of pneumonia is that which is known as *aspiration pneumonia* or *foreign body pneumonia*. It is produced by substances, such as food or foreign bodies of any sort, which are aspirated into the bronchi and alveoli, or both, and which produce foci of inflammation about them. The foci are most frequent in the lower lobes and there is usually an acute inflammation of the afferent bronchus. The exudate is usually purulent and there is a marked tendency to abscess formation and gangrene.

**HYPOSTATIC PNEUMONIA** appears most commonly in the posterior portion of the lower lobes of the lung, an infection being added to passive hyperæmia. The condition appears by preference in the course of severe and long continued infections, such as typhoid fever. The exudate is not abundant and contains few cells, other than red blood corpuscles, and usually little or no fibrin.

In acute interstitial pneumonia the interlobular septa of the lung are enlarged and pale and the consistency of the lung increased. It is due to infection of the lung by way of the interlobular lymphatics. In the interlobular tissue there is a purulent or fibrino-puru-

lent exudate which extends into the adjoining alveoli. The interlobular tissue may be involved in the course of both lobular and lobar pneumonia. When it arises, as an independent affection, it usually extends into the lung from the pleura and is most marked on the pleural surface. It is an uncommon condition and usually is due to infection with pyogenic cocci. In the chronic form of interstitial pneumonia the exudate may be replaced by fibrous cicatricial tissue.

**ATELECTASIS OF THE LUNG.** In atelectasis of the lung there is collapse of the air spaces, due to diminution or disappearance of the air content. The collapsed portions of the lung are depressed below the surface and deeply cyanotic. Two forms of this are recognized: (a) foetal atelectases in which the post-partum distension of the lung does not take place; and (b) acquired atelectases of which there are two forms, one, compression atelectasis, arising from compression of the lung from without, due to the collection of fluid or air or the presence of tumors in the pleural cavity, and the other, occlusion atelectasis, due to the occlusion of bronchi by secretion, exudation, foreign bodies, etc. The air, which is retained in the lung supplied by the closed bronchi, becomes absorbed and the alveoli collapse.

**EMPHYSEMA.** An increase in the air content of the lung is designated as *emphysema* and of this two forms, vesicular and interstitial emphysema, can be distinguished, depending upon whether the air is contained in the dilated alveoli, or in the interstitial tissue of the lung. Interstitial emphysema is due to rupture of the lung with the escape of the air into the interstitial tissue. The condition makes itself manifest on the pleural surface in the form of small bubbles of air in the interlobular septa; on pressure the tissue crackles beneath the fingers and the bubbles can be moved along. In marked conditions of interstitial emphysema the air passes from the hylum of the lung into the mediastinum and from this by way of the cervical fascia into the subcutaneous tissue. It may also pass more directly when there are pleuritic adhesions (see page 264).

**EXPERIMENTS.** The study of experimental conditions of the lungs and thorax include certain experiments in inflammation already taken up, the various forms of pleurisy. The production of pneumothorax by the injection of 500 c.c. air into the thorax of an anesthetized dog can be studied by observing the effect on respiration and blood pressure as indicated by the kymograph.

The trachea should be clamped before opening the thorax at autopsy so as to show the atelectasis of the lungs. The experiment can be repeated, using salt solution or olive oil instead of air, with the production of hydrothorax. Asthma is studied in the clinical manifestations of immediate anaphylaxis in the guinea pig and later studying the underlying acute emphysema. Œdema of the lungs (usually associated with hæmorrhage) can be produced by the injection into the posterior auricular vein of a rabbit of 0.7 c.c. 1: 1000 adrenalin solution. Acute bronchitis can be produced in the cat by the inhalation through a tracheal cannula of the fumes of strong ammonia. The physical signs are studied, especially with the multiple stethoscope (rales) and the autopsy performed to show the acute inflammatory process.

393 a

393 b



393 c

393 d

393 e

## STUDENTS' INDEX

## STUDENTS' INDEX

## STUDENTS' INDEX

## STUDENTS' INDEX

## STUDENTS' INDEX



## STUDENTS' INDEX

## INDEX

---

- A.
- Abortion, 220.
- Abcess, 50.  
     amœbic, 313.  
     cavity, 211.  
     formation, 203, 211.  
     healing, 212.  
     membrane pyogenic, 211.  
     metastatic, 213.  
     multiple, 213.  
     subcutaneous, 105, 213.
- Actinomycosis bovis, 280.
- Adaptation, 60, 194.
- Addison's disease, 37.
- Adenoma, 162.  
     adenocarcinoma, 166.  
     adenocystoma, 163.  
     adenofibroma, 151.  
     papilliferous, 163.
- Adrenal gland, accessory, 172.  
     carcinoma metastatic, 179.  
     lymphoma metastatic, 184.
- Albuminuria, 160, 349.
- Alexine, 199.
- Algor mortis, 41.
- Alimentary canal, 365.  
     experiments, 371.  
     snake venom, 370.
- Amboceptor, 199.
- Amyloid, 31.  
     degeneration, 267.  
     local formation, 33.
- Anæmia, 60, 305, 358.  
     pernicious, 61.  
     secondary, 61, 179.
- Anasarca, 93, 95, 97, 100, 362.
- Aneurysm, 80.  
     aorta, 118, 120, 121.  
     cirroid, 80.  
     dissecting, 81.  
     diffuse, 80.
- Aneurysm, *continued.*  
     miliary, 81, 275.  
     rupture, 118.  
     saccular, 80.  
     spindle form, 80.  
     tuberculous, 248.
- Anhydræmia, 62.
- Ankylostoma duodenale, 333.
- Anthrax, 285.  
     carbuncle, 285, 286.
- Antigen, 200.
- Antitoxin, 200.
- Appendix, appendectomy, 310.  
     appendicitis, 120, 366.  
     cystic dilatation, 121.  
     tuberculous, 262.
- Arteriosclerosis, 81, 97, 108, 113, 115,  
     118, 121, 172, 177, 227, 232,  
     267, 275, 362.  
     atheromatous ulcer, 78.  
     calcification, 78.
- Artery, 76.  
     coronary, sclerosis, 113, 367.  
     coronary, thrombosis, 115.
- Ascites, 93, 95, 100, 115, 362, 387.
- Atrium of infection, 204.
- Atrophy, 26.  
     from malnutrition, 26.  
     from pressure, 27.  
     from disuse, 27.  
     neuropathic, 27.  
     senile, 27.
- Autolysis, 53.
- Autopsies, 95, 97, 100, 105, 108, 112,  
     113, 115, 118, 120, 121, 172, 175,  
     177, 184, 187, 192, 213, 218, 220,  
     227, 229, 232, 237, 239, 262, 263,  
     266, 267, 275, 280, 282, 286, 292,  
     299, 303, 305, 310, 314, 319, 322,  
     326, 329, 358, 367, 374, 382,  
     386.

## B.

- Bacilli, 195.  
 Bacillus, anthracis, 285.  
   anthracis septicæmia, 286.  
   coli communis, 276, 310.  
   diphtheriæ, 290.  
   dysenteræ, 315.  
   mallei, 282.  
   tuberculosis, 243.  
 Bacteria, 195.  
 Bacteriolysis, 199.  
 Bile ducts, 260.  
   cholangitis, 310, 374.  
 Bilharzia Hæmatobium, 142.  
 Bilirubin, 38.  
 Biliverdin, 38.  
 Bladder, urinary, cystitis, 275.  
 Blood, 60.  
   coagulation, 62.  
   changes in malaria, 318.  
   experiments on, 69.  
   formation of, 24.  
   platelets, 63.  
   tumors, 159.  
   vessels, new formation, 53.  
 Body, general structure, 19.  
 Bone, regeneration, 130.  
   tuberculosis, 260.  
 Bone marrow, 179.  
   hyperplasia, 179, 358.  
   lymphoma metastatic, 184.  
 Brain, 91.  
   abscess, 221.  
   carcinoma metastatic, 175.  
   congestion, 232.  
   cyst, 97.  
   hæmorrhage, 97.  
   œdema, 362.  
   passive congestion, 91.  
 Breast, carcinoma, 175.  
 Bronchi, bronchitis, 121, 172, 322, 326.  
   bronchitis, tuberculous, 251.  
 Bronchioliths, 37.  
 Bronchopneumonia, 226, 276, 292,  
   326, 390.

## C.

- Cachexia, 139.  
 Calcification, 35.  
 Calculi, 36.  
   biliary, 36.

Calculi, *continued*.

- pancreatic, 36.  
   salivary, 36.  
   urinary, 36.  
 Capsule formation, 195.  
 Carbuncle, 212.  
 Carcinoma, 163.  
   adenocarcinoma, 166.  
   anæmia from, 179.  
   baso-cellulare, 165.  
   breast, 175.  
   colloid, 166.  
   cylindrical cell, 166.  
   en cuirass, 175.  
   epidermoid, 164, 165.  
     keratin formation, 165.  
   pearls, 165.  
   rodent ulcer, 166.  
   epithelial fibrils, 165.  
   glandular, 166.  
   medullary, 164.  
   pleura, 175.  
   scirrhus, 164.  
   stomach, 177.  
   ulceration, 175, 176.  
 "Carriers," 206.  
 Cases, 171, 175, 182, 183, 234.  
 Cell, endothelial, 56.  
   plasma, 56.  
   structure, 17.  
 Cestodes, 331.  
 Chemotaxis, 52.  
 Chemotropism, 52.  
 Chloroma, 160.  
 Cholera, 309.  
 Cholesteatoma, 169.  
 Cholesterin, 31.  
 Chondroma, 152.  
   chondrosarcoma, 153.  
 Chorio-epithelioma, 166.  
 Choroid plexus, cyst, 232, 374.  
 Circulation, 82.  
   experiments on, 82.  
   pathological physiology of, 84.  
 Cloudy swelling, 29.  
 Coagulation necrosis, 43.  
 Coliquation necrosis, 43.  
 Colloid degeneration, 34.  
 Colon, amœbic, dysentery, 314.  
   acute epidemic dysentery, 306.  
   necrosis, 305.

- Colon, *continued*.  
 perforation, 314.  
 ptosis, 172.  
 typhoid ulcer, 303.  
 ulceration, 305.  
 Complement, 199.  
 Concretion, 36.  
 intestinal, 37.  
 preputial, 37.  
 Condyloma, broad, 272.  
 Congestion, passive, 89, 95, 97, 108, 115.  
 Conjunctiva, acute conjunctivitis, 303.  
 Corpora amylacea, 35.  
 Crisis, 205.  
 Cyanosis, 88.  
 Cyclasterion scarlatinalis, 326.  
 Cysts, 147.  
 congenital, 147.  
 dermoid, 147, 169.  
 epidermoid, 169.  
 extravasation, 147.  
 exudation, 147.  
 kidney, 147.  
 retention, 147.  
 softening, 147.  
 Cytoryctes variolæ, 321.  
 Cysticercus cellulosa, 332.
- D.
- Defervescence, 205.  
 Degeneration, 29.  
 cloudy swelling, 29.  
 experimental, 44.  
 hyalin, 33.  
 hydropic, 33.  
 parenchymatous, 286, 292, 299.  
 vacuolar, 33.  
 Zenker's, 34.  
 Diabetes, 267.  
 bronze, 373.  
 Diapedesis, 47.  
 Diboethriocephalus latus, 331.  
 Diphtheria, 290.  
 bronchopneumonia, 291.  
 lesions, 290.  
 membrane, 290, 292.  
 mixed infection, 291.  
 Diplococcus intracellularis meningitidis, 235.  
 Diplococcus lanceolatus, 224.  
 Diplococcus pneumoniae, 224.  
 Disease, 17.  
 Distomata, 334.  
 Dropsy, 93.  
 Duct of Wirsung, concretion in, 374.  
 Dysentery, 305.  
 amoebic, 314.  
 diphtheritic, 305.  
 epidemic, 305.
- E.
- Ear, otitis media, 105, 220, 227, 229, 232, 326.  
 Ecchymoses, 92, 184.  
 Eclampsia, 44.  
 Embolism, 66, 108, 310.  
 air, 68.  
 fat, 68.  
 paradoxical, 66.  
 parenchymatous, 68.  
 Embryoma, 171.  
 Emigration, 47.  
 Emphysema, 186.  
 Empyema, 218.  
 Endocardium, 74.  
 endocarditis, chronic, 213.  
 endocarditis, 74, 95, 97, 100, 105, 172, 239.  
 thrombosis, 115.  
 Endometritis, 218.  
 Endothelioma, 154.  
 Endotoxins, 196.  
 Entamoeba histolytica, 313.  
 Ependymitis, granular, 267.  
 Epicardium, 71.  
 ecchymoses, 97.  
 lymphoma metastatic, 184.  
 Epididymis, tuberculous, 255, 267.  
 Erysipelas, 200.
- F.
- Fallopian tubes, gonorrheal, 238.  
 tuberculosis, 255.  
 Fat necrosis, 43, 374.  
 Fatty degeneration, 29.  
 Fastigium, 205.  
 Fibroblasts, 57.  
 Fibro-lipoma, 151.  
 Fibroma durum, 149.  
 fibrochondroma, 153.  
 fibroepithelium, 150.  
 intracanalicular, 151.

*Fibroma durum, continued.*

- keloid, 149.
- molle, 149.
- neuro, 149.

*Fibrosarcoma, 150.**Flukeworms, 334.**Furuncle, 212.*

## G.

*Gall bladder, cholecystitis, 310, 374.*  
*cholecystotomy, 374.**Gall stones, 36.**Gangrene, 44, 108.**Genitalia, tuberculosis, 254.**Genito-urinary system, tuberculosis,*  
*266.**Glanders, 282.**abscess formation, 282.**pustules, 282.**Glioma, 157.**Glios, 263.**Gluge's corpuscles, 31.**Glycogen, 31.**glycogenic degeneration, 267.**Glycosuria, experimental production,*  
*377.**Gonococcus, 238.**Gonorrhea, 238.**Gout, 40.**Granulation tissue, 53.**Growth, 124.*

## H.

*Hæmangioma, 154.**Hæmatin, 38.**Hæmatoidin, 38.**Hæmatoma, 92.**Hæmochromatosis, 38.**Hæmoglobin, 37.**Hæmoglobinæmia, 38, 62.**Hæmoglobinuria, 62.**Hæmolysis, 62.**Hæmolysin, 196.**Hæmorrhage, 374.**Hæmosiderin, 38.**Heart, 71.**aneurysm, 108.**dyspnœa, 88.**fatty degeneration, 181, 326.**hypertrophy, 74, 86, 97, 100, 108,**115, 275, 385, 386.**Heart, continued.**infarction, 87, 115.**insufficiency, 88.**perforation, 239.**rhabdomyoma, 142, 158.**thrombi, 115, 108, 326, 75.**valves, insufficiency, 85.**stenosis, 85.**Heredity, 206.**Hernia, 112.**Hormones, 125.**Hydræmia, 62.**Hydropericardium, 93, 95, 100, 115,*  
*232.**Hydrothorax, 93, 95, 100, 115, 121,*  
*362.**Hyperplasia, 124.**Hypertrophy, 124.**Hypoleukocytosis, 52, 125.**Hypoplasia, 26.*

## I.

*Ileum, dysenteric lesions, 306.**hæmorrhage, 189.**perforation, 108, 303.**tuberculous ulcer, 254.**typhoid ulcer, 299.**Immunity, 201.**Incrustation, 36.**Incubation, 205.**Infarction, 67.**red, 67.**uric acid, 347.**white, 67.**Infection, 194, 196.**atrium of, 204.**chronic, 204.**from conjunctiva, 197.**intestinal canal, 198.**lungs, 197.**middle ear, 197.**mouth, 197.**nasal passages, 197.**œsophagus, 198.**skin, 197.**stomach, 198.**tonsil, 197.**wounds, 198.**intra-uterine, 207.**multiple, 275.**post partum, 218.*

Infection, *continued*  
 secondary, 207.  
 terminal, 207.  
 variation in, 208.  
 Infectious diseases, 194.  
 experiments, 334.  
 Infestation, 194.  
 Inflammation, 46.  
 catarrhal, 50.  
 experiments, 58.  
 exudation, 48.  
   diphtheritic, 50.  
   fibrinous, 49.  
   haemorrhagic, 50.  
   purulent, 50.  
   serous, 49.  
 heat, 47.  
 pain, 50.  
 purulent infiltration, 187.  
 redness, 47.  
 swelling, 48.  
 Intestine, carcinoma metastatic, 179.  
   dysentery, 305, 314.  
   lymphoma metastatic, 184.  
   passive congestion, 91.  
   pathology of, 365 - 371.  
   perforation, 108, 303, 314.  
   tuberculosis, 256, 263.  
   typhoid lesions, 299.  
 Invasion, 205.  
 Involucrum, 212.

## J.

Jaundice, 39, 310, 374, 382, 286.

## K.

Karyolysis, 43.  
 Karyorhexis, 43.  
 Keloid, 149.  
 Keratitis, 203.  
 Kidney, 337.  
   albuminuria, 349.  
   arteriosclerosis, 344, 357.  
   atrophy, 356.  
   blood vessels, 337.  
   cantharadin, effects on, 364.  
   congestion, 386.  
     passive, 90.  
   cysts, 172.  
   decapsulation, 358.  
   double pelvis, 172, 369.

Kidney, *continued*.  
   embryoma, 171.  
   experiments, 364.  
   gout, 355.  
   granular contracted, 355.  
   hæmorrhage, 344.  
   hydronephrosis, 172, 344.  
   hyperæmia, acute, 343.  
     passive, 343.  
   infarction, 97, 115, 344.  
     bilirubin, 348.  
     uric acid, 347.  
   lymphoma metastasis, 184.  
   malformations, 340.  
   mercuric iodide, effects on, 364.  
   mixed tumor of, 171.  
   nephropathy, 108, 115, 172, 343.  
     acute capsular, 353.  
     acute diffuse, 350.  
     acute interstitial, 291, 326, 350.  
     acute intracapillary, 352.  
     chronic, 353, 358.  
     chronic diffuse, 355.  
     chronic interstitial, 355.  
     degenerative, 345.  
     desquamative, 348.  
     diffuse, 386.  
     infectious, 345.  
     obstructive, 344.  
     glomerular, 100, 352.  
       acute, 220, 218.  
       intracapillary, 362.  
     parenchymatous, 352.  
     subacute, 353.  
     vascular, 343.  
   nephrolithiasis, 345.  
   nephrophthisis, 256.  
   pathology of 337 - 364.,  
   potassium chromate effects, on,  
     363.  
   pyelonephritis, 345, 310.  
     tuberculous, 256, 276.  
   tuberculosis, 256.  
   uranium nitrate, 364.

## L.

Larynx, œdema, 97.  
   laryngitis, 322.  
 Lead poisoning, 40.  
 Leiomyoma, 153.  
 Leprosy, 270.

- Leukæmia**, 160.  
     lymphatic, 160.  
     myelogenous, 161, 187.  
**Lip**, epidermoid carcinoma, 171.  
**Lipochrome**, 37.  
**Lipoma**, 151.  
**Liver**, abscess, 310.  
     amœbic, 314.  
     acute yellow atrophy, 378, 382.  
     carcinoma metastatic, 179.  
     cirrhosis, 90, 100, 380, 386.  
         atrophic, 380.  
         cardiac, 90, 380.  
         hypertrophic, 381.  
         monolobular, 380.  
         multilobular, 380.  
     congestion, 172.  
         passive, 90.  
     experiments, 390.  
     lymphoma metastatic, 184.  
     leukæmia, 187.  
     necrosis, 43, 95, 305.  
         chloroform, 129.  
         focal, 220, 326.  
     nutmeg, 90.  
     pathology of, 378.  
     perihepatitis, 97, 100, 172.  
     regeneration, 128.  
     tuberculosis, 260, 262.  
**Livor mortis**, 41.  
**Liquefaction necrosis**, 43.  
**Lung**, abscess, 106, 187, 213, 218.  
     anthracosis, 314.  
     atelectasis, 121, 392, 393.  
     bronchopneumonia, 121.  
     bronchitis, 121.  
     carnification, 226.  
     coal miner's, 39.  
     congestion, 172, 213.  
     embolus, 112.  
     emphysema, 100, 184, 314, 392.  
     engorgement, 225.  
     experiments, 392.  
     hepatization, 225.  
     infarction of, 95, 97, 105, 108, 115, 213.  
     lymphoma metastatic, 184.  
     œdema, 176, 299, 305, 322, 362, 367, 386.  
     pathology of, 390.  
     pneumonia, (see pneumonia).  
     Lung, tuberculosis, 172, 176, 249, 262.  
     Lupus, 261.  
     Lymph nodes, hæmorrhage, 103.  
         lymphnoditis acute, 286.  
         metastatic carcinoma, 179.  
         syphilis of, 272.  
         tuberculosis, 173, 257, 263.  
         typhoid, 300.  
     Lymphangioma, 154.  
     Lymphatics, 160.  
     Lymphoma, 159, 184.  
         metastasis, 184.  
     Lysis, 205.
- M.
- Macrocheilia**, 154.  
**Macrogamete**, 318.  
**Macroglossia**, 154.  
**Macrophage**, 55.  
**Malaria**, 317.  
     chronic, 305, 306.  
     pernicious, 319.  
     pigment formation, 318.  
**Mastoid**, mastoiditis, 105, 220, 276.  
**Measles**, 325.  
     skin eruption, 325.  
**Mediastinum**, emphysema, 264.  
     mediastinitis, 322.  
**Membrana propria**, 162.  
**Meninges**, meningitis, 220, 229.  
     hæmorrhagic, 286.  
     epidemic cerebro-spinal, 235, 237.  
     tuberculous, 259, 262.  
**Merozoites**, 318.  
**Metaplasia**, 130.  
**Metastases**, 164.  
**Methæmoglobin**, 38.  
**Metritis**, 218.  
**Microgamete**, 318.  
**Microphage**, 55.  
**Milzbrand**, 285.  
**Mitosis**, 124.  
**Mole hydatidiform**, 167.  
**Moulds**, 195.  
**Mucoid degeneration**, 32.  
**Muscle**, regeneration, 129.  
**Myocardium**, 73.  
     abscess, 73.  
     aneurysm, 74.  
     fatty degeneration, 73.  
     hyalin degeneration, 73.

*Myocardium, continued.*

- myocarditis, 108, 110, 113, 239, 367.
  - fibrous, 73.
  - necrosis, 73.
  - tubercle, 73.
- Myoma, uterus, 176.
- Myxoma, 151.
  - myxochondroma, 152.
- Myeloma, 160.

## N

- Nævus, 154.
- Necrosis, 41.
  - fat, 43.
  - liver, 43.
- Nematodes, 332.
- Nerves, neuroma, 149.
  - regeneration, 128.
- Neuro-epithelioma, 157.
- Neurofibroma, 149.
- Neuroglia, cell proliferation, 235.
- Neuroma, 157.
  - multiple, 149.
  - plexiform, 150.
- Nipple, retraction, 175.

## O.

- Ochronosis, 37.
- Œdema, 93, 115, 386.
  - cardiac, 94.
  - larynx, 97.
  - renal, 95.
  - subpial, 374.
  - tissue changes, 94.
- Œsophagus, carcinoma, 172.
  - penetration by tumor, 172.
  - smallpox, 322.
  - stricture, 172.
  - ulceration, 173.
- Oligæmia, 60.
- Oligocythæmia, 60.
- Omentum, metastatic carcinoma, 179.
- Onchosphere, 331.
- Oökinet, 318.
- Opsonins, 199.
- Osteoclasts, 130.
- Osteochondritis syphilitica, 274.
- Osteoma, 153.
  - eburneum, 153.
  - spongiosum, 153.
- Osteomyelitis, 212.

- Otitis media, 220, 227, 229, 232, 326.
- Ovary, metastatic carcinoma, 179.

## P.

- Pancreas, 372.
  - abscess, 372.
  - atrophy, 373.
  - calculi, 374.
  - carcinoma metastatic, 179
  - degeneration, 373.
  - diabetes, 373.
    - bronze, 373.
  - experiments, 377.
  - necrosis, 373.
  - pancreatitis, chronic, 100, 172.
    - acute hæmorrhage, 374.
    - gangrenous, 374.
    - purulent, 374.
  - secretion, 373.
  - structure, 372.
  - syphilis, 372.
  - tuberculosis, 372.
- Papilloma, 150.
- Parametrium, 219.
- Parasite, 194.
- Pediculi, 194.
- Penis, sarcoma, 183.
- Pericardium, hæmorrhage, 239.
  - pericarditis, 72, 239, 329.
- Perihepatitis, 172.
- Perithelioma, 156.
- Peritoneum, carcinoma metastatic, 179.
  - peritonitis, acute, 108, 303, 314, 367, 374.
    - amœbic, 314.
    - chronic, 113, 232, 275, 386.
- Petechiæ, 92, 184.
- Peyer's patch, typhoid, 301.
- Phagocytosis, 53, 54, 199.
- Pharynx, 97.
  - smallpox, 322.
  - ulceration in typhoid, 301.
- Phlebitis, 76, 101.
- Phleboliths, 37.
- Phthisis, 252, 262.
  - fibroid, 253.
  - tuberculous, 267.
- Pia mater, œdema, 97.
- Pigmentation, 37.
  - autochthonous, 37.



**Pigmentation, *continued*.**

- extraneous, 39.
- hæmatogenous, 38.
- malarial, 37.
- Placenta, syphilis, 274.
- Plasmodium malariz, 317.
- precox, 317.
- vivax, 317.
- Plethora, 62.
- Pleura, carcinoma, 175.
- pleuritis chronic, 97, 121, 175, 179, 213, 266, 267, 276, 367, 386.
- pleuritis acute, 227, 229, 232, 282.
- tuberculosis, 262, 266.
- Pneumococcus, 224, 326.
- Pneumonia, aspiration, 391.
- caseous, 251.
- catarrhal, 390.
- croupous, 232.
- acute, 225, 227.
- hypostatic, 391.
- interlobular, 391.
- interstitial, acute, 391.
- in cerebro-spinal meningitis, 236.
- leucocytosis, 227.
- lobar, acute, 225.
- lobular, 390.
- organizing, 226, 229, 232.
- resolution, 226.
- syphilitic, 274.
- tuberculous, 267, 251.
- unresolved, 229.
- Pneumothorax, 263, 392.
- Poliomyelitis, acute anterior, 329.
- lesions, 329.
- virus of, 329.
- Polypi, 150.
- Post mortem, 42.
- blood coagulation, 42.
- cell changes, 42.
- decomposition, 42.
- putrefaction, 42.
- Pott's disease, 261.
- Prostate, prostatitis acute, 239, 275.
- Protozoa, 195.
- Pus, 211.
- Pylephlebitis, 310.
- Pyknosis, 43.
- Pylorus, occlusion, 179.

**R.**

- Recovery, 206.
- Regeneration, 124.
- Repair, 52, 55.
- Resolution, 226.
- Rhabdomyoma, 158.
- Ribs, metastatic carcinoma, 179.
- Rigor mortis, 41.

**S.**

- Salpingitis, acute, 234.
- gonorrhœal, 238.
- Saprophyte, 206.
- Sarcoma, 155.
- giant cell, 156.
- melanotic, 182, 157.
- mixed cell, 156.
- osteo, 156.
- osteoid, 156.
- penis, 183.
- round cell, 156.
- spindle cell, 156.
- Scarlet fever, 326.
- Scharlach R., 30.
- Schistosomum hæmatobium, 334.
- Schizogamy, 318.
- Scrotum, teratoma, 192.
- Seminal vesicles, fasciculitis, 275.
- Septicæmia, 95.
- Sequestrum, 212.
- Skin, hyperæmia, 326.
- lupus, tuberculous ulcer, 261.
- regeneration, 128.
- syphilis, 272.
- tuberculosis, 261.
- anatomical ulcer, 261.
- Skull, teratoma, 192.
- Smallpox, 320.
- balanitis, 322.
- confluent, 320.
- discrete, 320.
- purpura variolosa, 320.
- pustulosa hæmorrhagica, 320.
- streptococcus infection, 324.
- Sodium urate, 40.
- Softening, puriform, 64.
- purulent, 64.
- Spirilla, 195.
- Spirillum cholerae asiaticæ, 309.
- Spleen, congestion, 386.
- acute, 382.

*Spleen, continued.*

- passive, 90.
  - hæmorrhage, 187.
  - infarction, 97, 105, 187.
  - leukæmia, 187.
  - lymphoma metastatic, 184.
  - perisplenitis, 97, 100.
  - chronic, 374.
  - swelling, acute, 105, 218, 227, 232, 286, 299, 303, 310, 367.
- Splenic fever, 285.
- Spores, 195.
- Sporozoite, 318.
- Staphylococcus aureus, 105, 211, 213.
- Sternum, erosion, 118, 212.
- carcinoma metastatic, 179.
- Stomach, carcinoma, 177.
- gastro-enterostomy, 179.
  - ulcer, 365.
- Streptococcus, 95, 105, 217, 276, 292, 326.
- septicæmia, 97, 263.
- Streptothrix actinomyces, 280.
- Structure, foam, 17.
- Susceptibility, 201.
- Symbiosis, 194.
- Syncytioma, 167.
- Synovitis, 239.
- Syphilis, 121, 271.
- amyloid disease, 273.
  - chancre, 271.
  - congenital, 273.
  - experiments, 275.
  - secondary infection in, 273.
  - vascular lesions, 273.

## T.

- Tænia echinococcus, 332.
- saginata, 331.
  - solium, 331.
- Tapeworms, 331.
- Tattooing, 39.
- Teratoma, 167, 169.
- congenital, 192.
  - scrotum, 192.
- Testicle, necrosis focal, 322.
- orchitis, chronic, 275.
- Tetanus, 201.
- Thoracic duct, tuberculosis, 248, 263.
- Thrombus, 42, 63.
- canalization, 64.

*Thrombus, continued.*

- hyalin, 63.
  - infection, 65.
  - mural, 64.
  - organization, 64.
  - red, 63.
  - tuberculous, 248.
  - white, 63.
- Thrombophlebitis, 105, 310.
- Thrombosis, 62, 101, 108, 112, 121, 189, 275.
- Thrush, 197.
- Tissue, cicatricial, 57.
- connective, 21.
  - fluid, 25.
- Tonsils, diphtheria, 292.
- tonsillitis, acute, 217.
  - tuberculosis, 254.
- Toxins, 196.
- Trachea, smallpox, 322.
- trachitis, 322.
  - tuberculosis, 254.
- Treponema pallidum, 271.
- Trichinella spiralis, 194, 333.
- Tubercle, conglomerate, 245.
- diffuse, 245.
  - miliary, 244.
  - structure, 245.
- Tuberculosis, 197, 200.
- aneurysm, 248.
  - bacillus, 243.
  - bile ducts, 260.
  - bladder, 257.
  - bones, 260.
  - brain, 259.
  - caseation, 247.
  - cicatrization, 246.
  - conglomerate tubercle, 245.
  - diffuse tuberculous tissue, 245.
  - disseminated, partial, 249.
  - exudate, 246.
  - genitalia, 254.
  - hæmorrhage, 253.
  - ileum, 187.
  - joints, 260.
  - kidney, 256.
  - larynx, 254.
  - liver, 260.
  - local, 249.
  - lung, 249, 172, 176, 262.
  - healed, 115.

*Tuberculosis, continued.*

- meninges, 259.
- miliary, acute, 263, 266.
  - chronic, 249.
  - disseminated, 249.
  - general, 248.
  - tubercle, 244.
    - structure, 244.
  - tuberculosis, acute, 261.
- mode of infection, 243.
- mucous membrane, 254.
- nephrophthisis, 256.
- phthisis, 252, 267.
- relation of tubercle bacilli, 246.
- serous surfaces, 258.
- skin, 261.
  - anatomical tubercle, 261.
  - lesions in miliary tuberculosis, 261.
  - tuberculous ulcer, 261.
- softening, 247.
- susceptibility, 244.
- thoracic duct, 248.
- tissue resistance, 244.
- tubercle, solitary, 260.
- trachea, 254.
- tuberculous bronchitis, 251.
  - peribronchitis, 251.
  - pneumonia, 251.
  - thrombi, 248.
- ulcer, 254.
  - primary, 187.
- ureter, 257.
- urinary system, 256.

*Tumors, 131.*

- adaptation, 139.
- adenoma, 145.
- ætiology, 145.
- angioma, 145.
- benign, 143.
- blood, 159.
  - supply, 133.
- cachexia, 139.
- carcinoma, 145.
- cell inclusions, 141.
- chloroma, 145.
- chondroma, 145.
- chorio epithelioma, 145.
- classification, 143, 145.
- Cohnheim theory, 143.
- cystic, 148.
- degeneration, 137.

*Tumors, continued.*

- embryoma, 145, 171.
- endothelioma, 145.
- environment, 139.
- epithelial, 162.
- experimental, 146, 193.
- fibro-epithelial, 150.
- fibroma, 145.
- frequency, 141.
- glioma, 145.
- hypernephroma, 145.
- immunity, 146.
- infection, 140.
- inheritance, 140.
- intercellular substances, 133.
- leiomyoma, 145.
- leukocytoma, 145.
- lipoma, 145.
- lymphoma, 145.
- malignant, 143.
- melanoma, 145.
- metaplasia, 142.
- metastases, 135.
- mixed, 170.
- myeloma, 145.
- myoma, 145.
- myxoma, 145.
- necrosis, 137.
- neuroma, 145.
- of animals, 146.
- origin, 133.
- osteoma, 145.
- papilloma, 145.
- rhabdomyoma, 145.
- sarcoma, 145.
- size, 131.
- structure, 132.
- teratoma, 145.
- thrombi, 135.
- tissue changes, 134.
- Typhoid fever, 298, 299, 303.
  - endothelial cell, 298.
  - infection, 298.
  - phagocytosis, 298.
  - perforation of intestine, 303.
  - ulceration of colon, 303.
  - ulcer of pharynx, 303.

## U.

- Ulcer, rodent, 166.
- Uncinaria americana, 333.

Ureter, double, 367.  
     malformation, 341.  
 Urethra, smallpox, 322.  
     stricture, 275.  
     urethritis, acute, 239.  
         chronic, 275.  
 Urinary system, tuberculosis, 256.  
 Uterus, myoma, 176.

V.

Vaccinia, 321.  
 Variola, 320.  
 Vasa deferentia, 267.  
 Veins, 76.  
     thrombophlebitis, 105, 310.  
     thrombi, 63.  
 Vertebrae, erosion, 120.

Vesiculæ seminales, tuberculosis, 255.  
 Vessels, blood, 20.  
     lymphatics, 20.  
 Virulence, 208.

W.

Wassermann reaction, 275.  
 Wool sorter's disease, 285.  
 Worms, parasitic, 331.  
     tape, 331.

X.

Xanthoma, 152.

Y.

Yeasts, 195.







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